R
11
A87
v.20
no.3
Biological
& Medical
Serials

SCIENCE & MEDICINE DEPT.
Duplicate

VOLUME 20 NUMBER 3

THE ARCHIVES OF INTERNAL MEDICINE

STORAGE

EDITORIAL BOARD

JOSEPH L. MILLER, Chicago

RICHARD C. CABOT, Boston
THEO. C. JANEWAY, Baltimore
GEORGE DOCK, St. Louis
WARFIELD T. LONGCOPE, New York
W. S. THAYER, Baltimore

LIBRARY
APR 16 1974
UNIVERSITY OF TORONTO

SEPTEMBER 15, 1917

CHICAGO
AMERICAN MEDICAL ASSOCIATION
PUBLISHERS

ENTERED AS SECOND-CLASS MATTER, JANUARY 23, 1909, AT THE POSTOFFICE AT CHICAGO, ILLINOIS, UNDER ACT OF CONGRESS OF MARCH 3, 1879

CONTENTS OF VOLUME XX

JULY, 1917. NUMBER 1

PAGE

THE PULSE FLOW IN THE BRACHIAL ARTERY. V. THE INFLUENCE OF CERTAIN DRUGS. ALBION WALTER HEWLETT, M.D., SAN FRANCISCO..... 1

STUDY OF A CASE OF DIABETES INSIPIDUS WITH SPECIAL REFERENCE TO THE MECHANISM OF THE DIURESIS AND OF THE ACTION OF PITUITARY EXTRACT ON IT. C. D. CHRISTIE, M.D., AND G. N. STEWART, M.D., CLEVELAND.. 10

MULTIPLE HEMANGIOMAS OF THE SKIN ASSOCIATED WITH DYSPITUITARISM. GEORGE DOUGLAS HEAD, B.S., M.D., MINNEAPOLIS..... 24

PHTHISIS PULMONALIS AND OTHER FORMS OF INTRATHORACIC TUBERCULOSIS. W. A. GEKLER, M.D., CHICAGO..... 32

THE STUDY OF A SMALL OUTBREAK OF POLIOMYELITIS IN AN APARTMENT HOUSE, OCCURRING IN THE COURSE OF AN EPIDEMIC IN A LARGE CITY. MONTROSE T. BURROWS, M.D., AND EDWARDS A. PARK, M.D., BALTIMORE 56

THE INFLUENCE OF SPLENECTOMY ON METABOLISM IN ANEMIA. W. DENIS, BOSTON 79

THE ELECTROCARDIOGRAM; ITS RELATION TO CARDIODYNAMIC EVENTS. CARL J. WIGGERS, M.D., NEW YORK..... 93

STUDIES OF THE BLOOD IN BERIBERI. I. YOSHIKAWA, K. YANO AND T. NEMOTO, TOKYO, JAPAN..... 103

A STUDY OF RENAL FUNCTION IN PATIENTS CONVALESCING FROM ACUTE FEVERS. ARTHUR BOOKMAN, M.D., NEW YORK..... 112

HEART BLOCK ASSOCIATED WITH HIGH BLOOD PRESSURE. JOHN H. MUSSER, JR., M.D., PHILADELPHIA..... 127

STUDIES IN THE VARIATIONS OF THE TONUS OF THE GASTRIC MUSCULATURE IN HEALTH AND DISEASE. BURRILL B. CROHN, M.D., AND ABRAHAM O. WILENSKY, M.D., NEW YORK..... 145

AUGUST, 1917. NUMBER 2

PAGE

AN ERROR IN THE ELECTROCARDIOGRAM ARISING IN THE APPLICATION OF THE ELECTRODES. HAROLD E. B. PARDEE, M.D., NEW YORK..... 161

STUDIES IN PROTEIN INTOXICATION. I. BLOOD COAGULATION. HOWARD F. SHATTUCK, M.D., NEW YORK..... 167

EMETIN DIARRHEA—CLINICAL AND EXPERIMENTAL. A. R. KILGORE, M.D., AND J. H. LIU, M.D., SHANGHAI, CHINA..... 178

STUDIES ON THE OXIDASE REACTION OF THE CELLS IN NORMAL AND LEUKEMIC BLOOD. N. ROSENTHAL, M.D., NEW YORK..... 184

RELATION OF PELLAGRA TO LOCATION OF DOMICILE IN SPARTAN MILLS, S. C., AND THE ADJACENT DISTRICT. J. F. SILER, M.D., P. E. GARRISON, M.D., AND W. J. MACNEAL, M.D., NEW YORK..... 198

The Archives of Internal Medicine

Vol. XX SEPTEMBER, 1917 No. 3

THE ETIOLOGIC AGENT OF RAT BITE DISEASE

PRELIMINARY REPORT *

J. KITAGAWA, M.D., AND T. MUKOYAMA, M.D.

That there exists a particular form of disease due to rat bite has been long recognized in Japan, where incidents of rat bite have been more frequent than in certain other countries. Although some cases have been reported by American, as well as French, German, British and Spanish physicians, yet the establishment of a definite disease as a result of rat bite has been chiefly the work of Japanese observers. Miyake[1] and Crohn[2] have given exhaustive reviews of the subject, together with their own case reports.

As to the etiologic agent, Ogata[3] thought it to be an organism belonging to the *Sporozoa,* while in German cases, the association of a streptothrix was reported by Schottmüller.[4] In a recent article, Blake[5] reports having obtained a pure culture of *Streptothrix muris ratti* of Schottmüller from a case of rat bite, by means of which he was able to reproduce in some rats local inflammation and proliferative lesions at the site of inoculation. The organism was nonpathogenic for guinea-pigs. Tileston[6] adds two cases of rat bite, in the blood smears from one of which he found a streptothrix, while the second case failed to show any such organism. Recovery followed the injection of salvarsan in these cases. It may be recalled that as early as 1912, Hata[7] recorded a series of cases of rat bite fever where the intravenous administration of salvarsan at the febrile stage of the disease led to a complete and permanent cure in all but two instances, in which a second injection was required during the relapses. Of special significance is the recent

* Submitted for publication Jan. 26, 1917.

* From the Pathological Institute of the Medical School of Nagoya, Japan.

* This work was done under the direction of Prof. Dr. Hayashi.

* An abstract of this paper was published in Japanese Feb. 12, 1916, in Chuo-Igakkai.

1. Miyake, H.: Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1900, **5,** 231.
2. Crohn, B. B.: THE ARCHIVES INT. MED., 1915, **15,** 1014.
3. Ogata: Deutsch. med. Wchnschr., 1908, **34,** 1099.
4. Schottmüller, H.: Dermat. Wchnschr., 1914, **58,** Supplement, 77.
5. Blake, F. G.: Jour. Exper. Med., 1916, **23,** 39.
6. Tileston, W.: Jour. Am. Med. Assn., 1916, **66,** 995.
7. Hata, S.: München. med. Wchnschr., 1912, **59,** 854.

discovery by Futaki[8] and his collaborators of a spirochete in the blood, as well as in the pathologic products, of patients suffering from rat bite fever. The spirochete was pathogenic for guinea-pigs and could be transmitted from man to this animal directly. As the occurrence of a spirochete has been revealed so far only in Japanese cases, it will be of interest to add another instance where apparently the same spirochete has been isolated. Below we give a brief report of our case, together with a description of the organism found therein.

On the night of Oct. 30, 1915, the mother of one of us attempted to catch a rat by shutting it up in a room. When she seized the rat, which she supposed to be dead, the animal bit her left index finger. The lesion, which bled slightly at first, later on began to swell and cause slight local pain. When the pain grew worse, we made a slight incision at the site of injury. Although no pus appeared to be present, the swelling continued for some days. The patient's temperature, which from the first was taken daily, never exceeded normal.

On the night of November 21, fever set in, accompanied by chills. The left axillary gland became swollen, and a large bright area of redness appeared, which extended from the outer surface of the forearm to the inner surface of the upper arm. The fever had already subsided by the next morning, and the red mark remained only a short time. This attack was followed by a recurrence of febrile periods at intervals of four or five days, accompanied by severe thirst and by variously formed itching red marks on the skin which alternately appeared and disappeared. The phenomena convinced us that the case was one of rat bite fever, and we examined preparations of the blood taken from the red marks but we failed to find any microorganism. Because of the conditions existing in the axillary lymph glands, they were extirpated during one of the febrile attacks, and inoculations were made into a monkey and several guinea-pigs and white rats. Examination of the tissues was made by dark field cultures and silver impregnations. The plasma which remained in the wound after the removal of the lymph gland and also the venous blood were removed and injected subcutaneously into guinea-pigs.

The injected monkey showed fever on the tenth day after inoculation and the guinea-pigs on the eleventh day. The febrile phenomena were almost identical with those presented by the patient, the fever returning every four or five days. We examined the lymph glands of the monkey and white rats, but nothing was found.

In January, 1916, the patient developed inflammation of the kidney. This suggested the removal of the kidney, liver, heart and spleen of the inoculated guinea-pigs, and on making smears of these (stained by Giemsa), we discovered in each organ spirochetes of a large type, such as are shown in Figures 1 and 2. The following day we examined smears of the internal organs and salivary glands of the inoculated white rats and found spirochetes of a smaller type, as shown in Figures 3 and 4. We examined also the internal organs of the inoculated monkey, without, however, detecting any microorganisms. But examination of the internal organs of the guinea-pigs injected with blood and plasma disclosed spirochetes identical with those found in the guinea-pigs injected with portions of the lymph gland. For the sake of convenience, we will designate the spirochetes found in the guinea-pigs as Type A, and those found in the white rats as Type B.

That the greatest number of spirochetes was found in the kidneys of the animals is noteworthy in view of the fact that the patient was suffering from nephritis.

---

8. Futaki, Takaki, Taniguchi and Osumi: Jour. Exper. Med., 1916, **23,** 249.

A point of significance in connection with the mode of infection in rat bite disease is the fact that the spirochete itself was found in small numbers in the salivary glands of the rats. These spirochetes, as well as those of Type A, usually show from four to eight curves. Some, however, have but from two to three curves, while others have as many as from nine to ten. As a rule, the curves of these spirochetes are regular, looser than those of the *Spirochaeta pallida,* more sharply defined than those of *S. refringens,* and more numerous than the Weil variety (Inada). The body of our spirochete is pointed at both ends and uniformly thick in the middle. It is much shorter and thicker than *S. pallida* and shorter than *S. refringens.* Most of the spirochetes of Type A are from 6 to 10 microns in length, although the smaller ones are 4 and the larger ones 12 microns long (Fig. 5). Most of the specimens of Type B are shorter than those of Type A, that is, from 3 to 5 microns, but some are only 2 and others vary from 6 to 7 microns in length. Both types show practically the same number of spirals and also nearly the same shape, but Type B appears in general to have sharper curves and to be less pointed at the ends, but some specimens closely resemble Type A. Nevertheless, the spirochete of Type B has always a smaller body than that of Type A and it is not difficult to recognize to which type a given specimen belongs.

More investigations will be necessary in order to determine definitely whether these spirochetes which show such differences with respect to size constitute one or two groups. It is a question whether these differences in size do not rather proceed from the differences of the inoculated animals or of the varying period of development of the spirochetes, as occurs in the case of bacteria and parasites. For further investigation of this question, we injected ordinary guinea-pigs and white rats with the spirochete-containing organs of the inoculated guinea-pigs, some of which had been subjected to Roentgen-ray treatment after undergoing preliminary splenectomy.

On examining the internal organs of all the white rats and guinea-pigs, we found not only that the spirochetes appeared in greater numbers in the animals that had undergone splenectomy than they did in the animals not so treated, but that they had become more pointed at the ends and had acquired looser curves. On the whole, Type B appeared to have somewhat approximated Type A.

The last examination showed the interesting phenomenon of two spirochetes of Type B having become so closely connected that they appeared to be one specimen in the process of undergoing division. Some seemed to be on the point of separating and remained connected only by means of very fine colorless threads; others apparently had

become quite detached from one another. Two spirochetes thus connected usually occupied a continuous line, but in some cases they formed an angle. Each of them was invariably small, from 2 to 3, or, in rare instances, 4 microns long; consequently, the number of spirals was also small. The specimens had usually from two to four and sometimes five spirals. It looked as if those specimens that possessed numerous spirals had been divided into two (Figs. 6, 7 and 8).

It was always quite uncertain in which of the internal organs the above-mentioned spirochetes were most frequently found. The fact that our patient had an unmistakable nephritis, and that after temporary recovery, there was a relapse, this attack being accompanied by enlargement of the liver, added to the fact that another patient of ours had had an attack of rat bite disease attended by cardiac paralysis, strongly suggests to us that every internal organ of man is subject to invasion by this spirochete, just as was the case with the experimental animals, no real differentiation between the pathologic processes in man and in the experimental animals being distinguished.

In our staining, in addition to the old and new Giemsa stain and Prof. Matsuura's modification of Levaditi's silver impregnation method, we successfully employed red-methyl-brown, a Giemsa-like fluid now being perfected by Segawa; also azulin, fuchsin, methyl-brown, gentian violet, etc. None of these methods disclosed any great difference between Types A and B.

We carried on control tests in ten healthy guinea-pigs, ten white rats and six house rats. In a kidney preparation of one of the house rats we discovered only one typical spirochete of Type B. In the salivary glands of one of the white rats and in one house rat we found spirochetes more than 20 microns in length. These spirochetes possessed regular curves and resembled *S. refringens.*

We now wish to consider whether our spirochete is really identical with the etiologic agent of rat bite fever.

It must first of all be stated that the disease is characterized by repeated attacks. There are two kinds of diseases caused by protozoa, those in the first class run a swift course, such as relapsing fever and malaria, those of the second group assume a chronic form which in some cases is very extreme; they are characterized by a recurrence of attacks during several subsequent years. According to Prof. Kusunoki, one or two yearly relapses occur for ten years after recovery from rat bite disease. Recently we saw a patient who still suffered recurrences fifteen years after the first attack of the disease. The fact that these attacks recur for as long as ten years appears to prove conclusively that the immunity against the agent is incomplete, and this leads us to

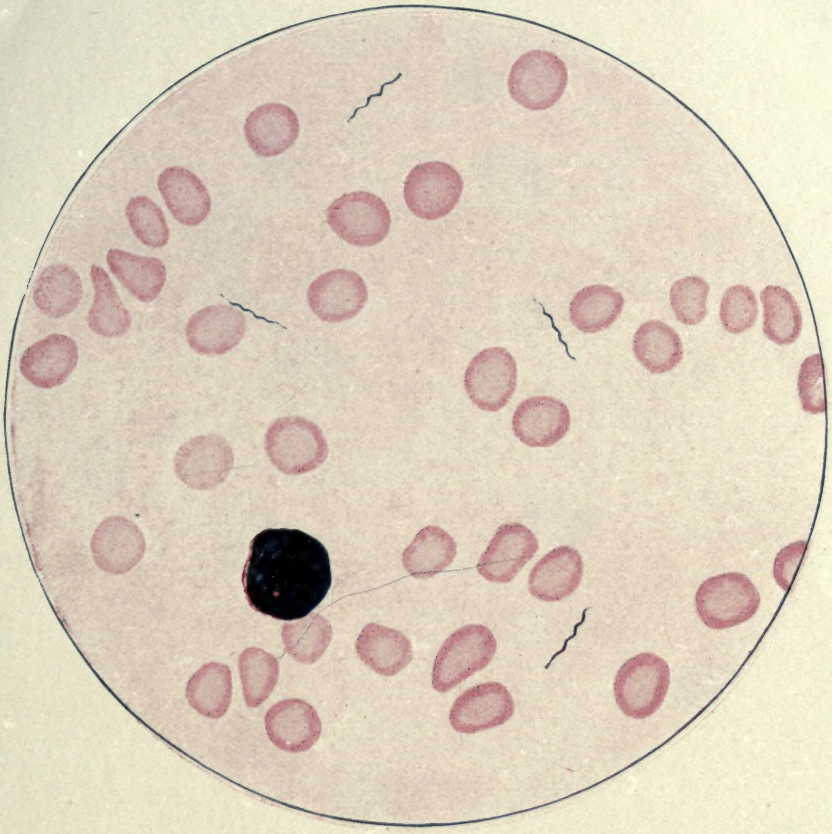

Fig. 1.—Giemsa-stained smear of kidney of guinea-pig inoculated with axillary gland of patient (Spirochete of Type A).

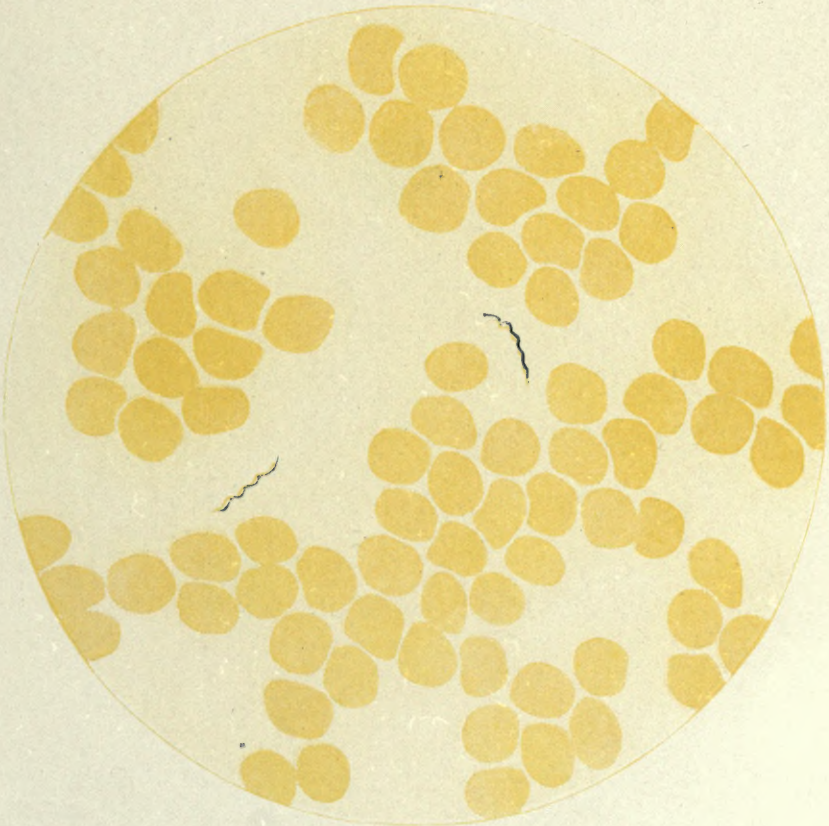

Fig. 2.—Silver impregnation of heart's blood of the same guinea-pig (Spirochete of Type A).

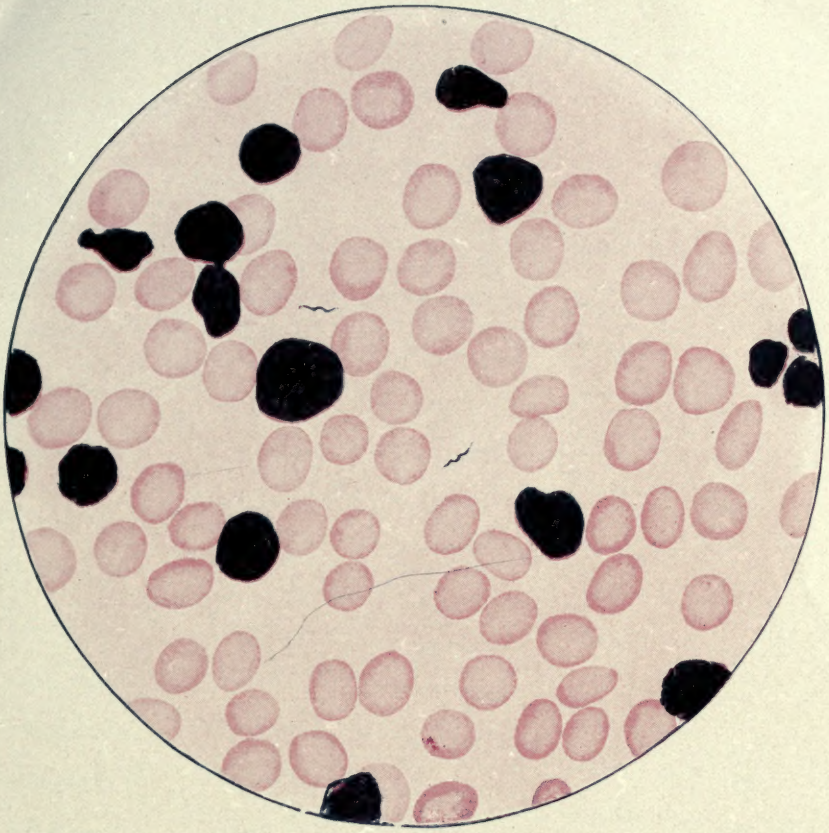

Fig. 3.—Giemsa-stained smear of kidney of white rat inoculated with patient's axillary gland (Type B).

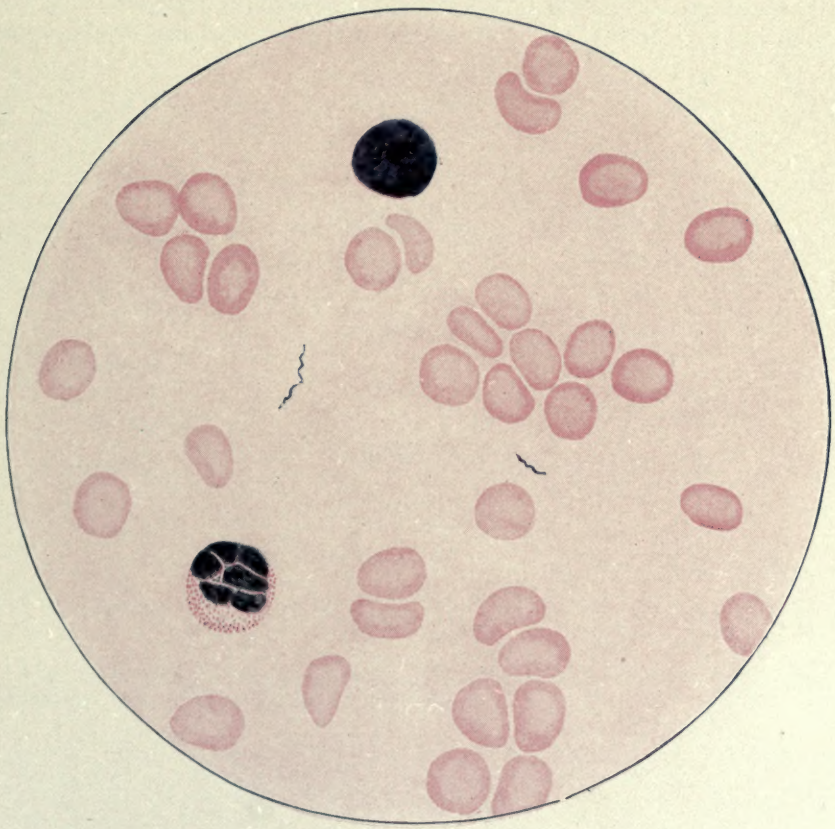

Fig. 4.—Giemsa-stained smear of liver of same white rat (Type B).

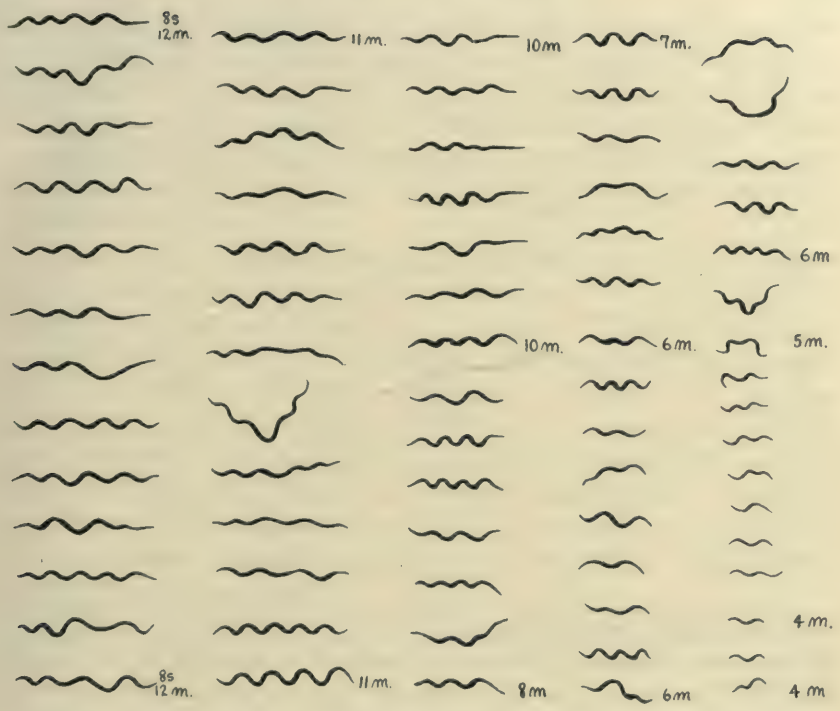

Fig. 5.—Principal forms of spirochetes of Type A found in the organs of the inoculated guinea-pig; *s*, spiral; *m*, micron.

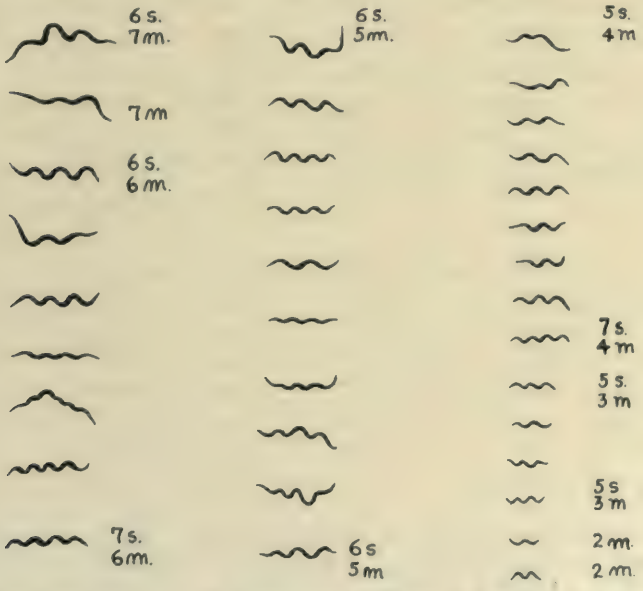

Fig. 6.—Principal forms of spirochetes of Type B found in the organs of the inoculated white rat; *s*, spiral; *m*, micron.

Fig. 7.—Spirochetes of Type B, obtained by inoculation of the splenectomized white rat (after previous subjection to Roentgen-ray treatment) with portions of the organs of another white rat containing spirochetes of Type B; *s*, spiral; *m*, micron.

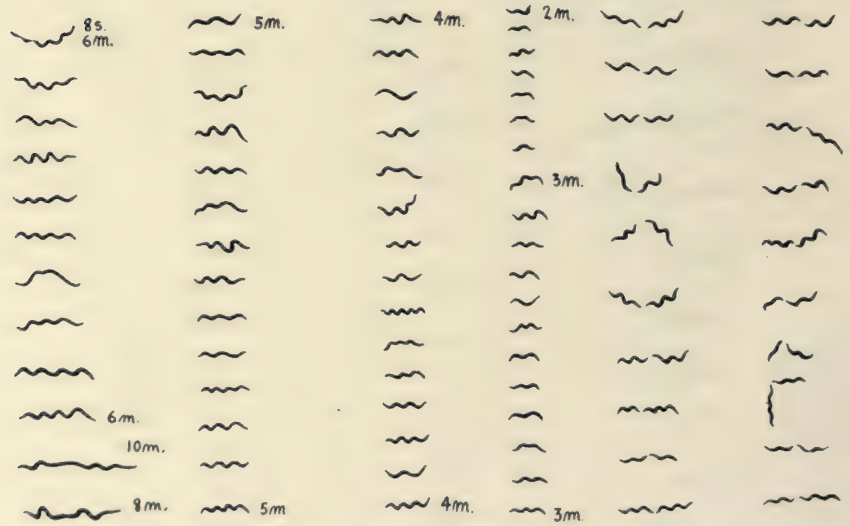

Fig. 8.—Varieties of form of spirochetes of Type B, obtained by inoculation of the splenectomized guinea-pig with the same organs as in Figure 4, 2, after previous subjection to Roentgen-ray treatment; *s*, spiral; *m*, micron.

conclude that the agent belongs to the group of protozoa that undergo gradual but marked modification with regard to form and toxicity. Moreover, since there is a definite period of incubation, followed by an eruption and swelling of the lymph glands, and since arsenic, especially salvarsan, is very efficacious in the treatment of the disease, our opinion is confirmed that we are dealing with a protozoan of the spirochetal variety.

The literature on the Wassermann reaction states that the reaction is positive in the case of such spirochetal diseases as relapsing fever, malaria, frambesia tropica and oriental sore. Dr. Kusunoki's experiments with this reaction, however, in five cases of rat bite fever showed it to be negative in four cases and positive in but one. It is possible, of course, that the latter subject had contracted a syphilitic infection at some time in the past. According to personal information received from Dr. Inada, the Wassermann reaction was negative in each of three cases of Weil's disease. It seems, therefore, that in rat bite disease and in some other spirochetal diseases we cannot place any reliance on the Wassermann reaction.

Repeated testing of the Wassermann reaction in one patient produced negative results. We therefore made an alcohol extract of the liver and heart of guinea-pigs harboring spirochetes of Type A, with which we made complement fixation tests. The complement fixation test was carried out twice in the case of a patient afflicted with rat bite fever with positive results. We applied the Wassermann reaction which also was positive. Subsequently, in order to prove whether or not our spirochetal antigen possessed any special peculiarity, we undertook experiments in complement fixation on patients suffering from rectal cancer, syphilis, and other similar diseases, at the same time applying the Wassermann test. The results of these experiments are given in the accompanying table.

RESULTS OF EXPERIMENTS IN COMPLEMENT FIXATION

Patient	Disease	Wassermann Reaction	Control	Reaction Spiro. Antigen	Control
Monkey.....	R. b. disease	±	±		
K.....	R. b. disease	—	—		
K.....	R. b. disease	+	—	+	—
K.....	R. b. disease	+	—	+	—
S.....	Rectal cancer	—	—	—	—
G.....	Syphilis	+	—	—	—
K.....	Syphilis	—	—	—	—
S.....	Syphilis	—	—	—	—
K.....	Syphilis	+ +	—	—	—
S.....	Syphilis	+	—	—	—
Y.....	Parenchymatous keratitis	—	—	—	—

It will be noticed that the reaction to the antigen of the spirochete of Type A proved positive in one case of rat bite disease.

Our organism of Type A not only possesses more spirals than does the spirochete discovered by Dr. Futaki in preparations stained with India ink but its curves are also much more regular. In comparison with those discovered by Dr. Futaki, the majority of our spirochetes, which are found in great quantities in our preparations, appear to belong to a different species. Yet they are nearly of the same size; moreover, irregularly shaped spirochetes, having fewer curves, were occasionally found in our preparations, so we at first concluded that Type A was of the same species as Dr. Futaki's spirochete. But another preparation of the variety discovered by Dr. Futaki, stained by the silver impregnation method of Levaditi, which had been found in the lymph gland of a patient, was exhibited at a meeting of the Pathological Society of Tokio, and from this specimen we were able to determine that these spirochetes were different from Type A. The organisms of Type B, however, seem to be identical with Dr. Futaki's specimen and also with those discovered at the same time by Dr. Ishiwara.

SUMMARY

The two types of spirochetes, found in the guinea-pigs and rat, respectively, not only varied considerably with respect to size, but also showed differences with regard to the distinctness of the spirals and the pointedness of the ends, which facts seem to us to indicate that these spirochetes belong to two different species. Yet, since the staining brought out no definite distinctions between them, and as they showed practically the same number of curves, it appears possible that the above-mentioned difference of form was a result of the differences existing between the inoculated animals, or that the spirochetes may have been in different stages of development. At all events, it is interesting to note that the spirochetes obtained from inoculation with the lymph gland and the lymph plasma derived from the same patient also appear to be of different sizes. Whether Type A and Type B are really identical, or, if they are not, which one is the etiologic agent, are points which cannot be determined without further investigation.

THE SALICYLATES

VIII. SALICYL EDEMA *

P. J. HANZLIK, M.D., R. W. SCOTT, M.D.
AND
J. L. REYCRAFT, M.D.
CLEVELAND

Following the administration of full therapeutic doses of salicylate there is a rather marked diminution in urine output, reaching its greatest depression about ten to twenty hours after the symptoms of toxicity appear and persisting for about forty to seventy hours after the administration of the drug. The output of urine reaches its previous level roughly about the time excretion of salicyl is completed.

Two possible explanations are suggested for this: (1) sweating; (2) retention of water, that is, edema; the important factors to be considered in retention are (*a*) tissues, and (*b*) kidney.

It is the object of this communication to report certain facts bearing on these causes. The work was conducted in a quantitative way and on persons some of whom were practically normal, others convalescent from various disorders. The following procedures were carried out before and after the administration of the salicylate, and throughout the experiment, which usually lasted about a week. The persons were weighed regularly, about three times in ten hours, and the drug was not administered until the weight curve became practically constant. This was reached usually within two to three days after the person was put to bed and placed on the regular routine. The water and dietary intakes were maintained as constant as possible throughout the procedure. Two hundred c.c. of water were administered every two hours. Coffee or milk was substituted for this at meal times. The meals were taken at the same hours, and the quantity was constant throughout. The administration of salicyl was so timed that the symptoms of toxicity would come when the stomach would be empty so as to avoid loss of contents in case emesis should occur. No attention was paid to the qualitative nature of the dietary, but even in this there were no radical changes, since the food in this hospital is remarkably constant in quality at all times.

* Submitted for publication April 14, 1917.
* From the Pharmacological Laboratory, Western Reserve University and the Medical Clinic, City Hospital, Cleveland.
* This investigation was supported, in part, by a grant from the Therapeutic Research Committee of the Council on Pharmacy and Chemistry of the American Medical Association.

Renal function was studied by the output of urine, which was collected in ten-hour periods; the quantitative excretion of albumin (method of Folin and Denis[1]); and daily observations on the phenolsulphonephthalein excretion (two-hour, and carried out in the usual way) and urea nitrogen of the blood (by the urease, aeration and colorimetric procedure). Hemoglobin estimations were made with the idea of ascertaining the chief depot of the water retention, that is, whether the blood or tissues. For this, the carbon monoxid colorimetric method of Haldane[2] was chosen, using the Duboscq colorimeter for making the readings instead of test tubes. The results are expressed as relative percentages of hemoglobin. The effect on and the rôle of the tissues were also judged, in part by the course of salicyl excretion in the urine. The salicyl was estimated according to a method previously described.[3] Sweating was judged, in part, from the weight curve and, in part, by direct inspection and the subjective symptoms reported by the patient himself.

When the weight and urine curves became practically constant, the salicylate was administered. A definite quantity (20 c.c.) of sodium salicylate (usually about 10 per cent.) was administered together with 80 c.c. of water every hour until toxicity, when the administration was stopped. The water intake was then maintained at the rate of 200 c.c. every two hours, and the various observations according to the procedures detailed above were carried out until the end of the experiment. In all, nine persons have been studied. Four of these (Patients 27, 28, 29 and 30) received sodium bicarbonate together with the salicylate. The detailed protocols for each individual are so long that they have been omitted entirely, and instead the data are presented in the form of curves for each one. Various clinical data pertaining to all the individuals are presented in the accompanying table.

1. *Salicylate Causes Edema.* — This is indicated by the fact that there is an increase in body weight demonstrable after the administration of the drug, unless this is prevented by sweating. Charts 1, 2, 3, 4, 6, 7 and 9 indicate definite increases in body weight and above the level before the drug was administered. This increase ranges from moderate to considerable. The diaphoresis ranged from imperceptible to just perceptible, and roughly, inversely proportional to changes in the body weight. That is, a relatively small diaphoresis is accompanied by a more marked increase in body weight.

Charts 5 and 8 show practically no changes in body weight. These persons gave evidences of marked diaphoresis. So far as other phe-

1. Folin and Denis: Jour. Biol. Chem., 1914, **18,** 273.
2. Haldane: Jour. Physiol., 1901, **26,** 497.
3. Thoburn and Hanzlik: Jour. Biol. Chem., 1915, **23,** 163.

TABLE OF CLINICAL DATA

Number and Patient	Diagnosis	Fluid and Dietary Intake	Total Quantity of Salicyl* Administered (gm.)	Diaphoresis	Remarks
21b (J. V.)	Normal; recovered from rheumatic fever	100 c.c. every hour for 5 hours 200 c.c. every 2 hours thereafter 384 gm. food 3 times daily	9.5	Imperceptible	
23 (J. E.)	Synechia cordis; chronic myocarditis	100 c.c. every hour for 5 hours 200 c.c. every 2 hours thereafter 384 gm. food 3 times daily	9.5	Marked	
24 (J. H.)	Chronic endocarditis and myocarditis	100 c.c. every hour for 5 hours 200 c.c. every 2 hours thereafter 320 gm. food 3 times daily	8.1	Mild	
25 (H. V.)	Catarrhal conjunctivitis	100 c.c. every hour for 5 hours 200 c.c. every 2 hours thereafter 320 gm. food 3 times daily	9.0	Mild	
26 (R. H.)	Corneal ulcer (left eye)	100 c.c. every hour for 7 hours 200 c.c. every 2 hours thereafter 384 gm. food 3 times daily	12.6	Marked	
27 (J. M.)	Varicose ulcer of leg.....	100 c.c. every hour for 7 hours 200 c.c. every 2 hours thereafter 384 gm. food 3 times daily	12.6	Mild	14 gm. $NaHCO_3$ administered together with salicyl
28 (T. S.)	Alcoholic gastritis	100 c.c. every hour for 5 hours 200 c.c. every 2 hours thereafter 384 gm. food 3 times daily	8.01	Moderate	9 gm. $NaHCO_3$ administered together with salicyl
29 (L. K.)	Rheumatic fever (mild attack)	100 c.c. every hour for 5 hours 200 c.c. every 2 hours thereafter 384 gm. food 3 times daily	8.9	Marked	8 gm. $NaHCO_3$ administered together with salicyl
30 (H. M.)	Chronic arthritis	100 c.c. every hour for 8 hours 200 c.c. every 2 hours thereafter 384 gm. food 3 times daily	14.24	Just perceptible	15 gm. $NaHCO_3$ administered together with salicyl

* Expressed as salicylic acid.

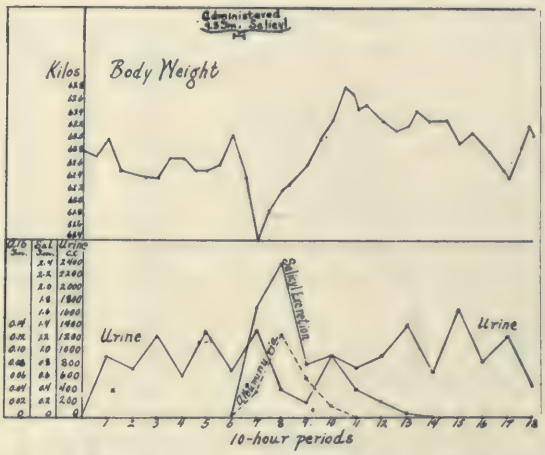

CHART 1.—Patient 21b (J. V.) In this and all the other charts the brace at the top of the chart indicates the period during which salicyl was administered; salicyl refers to salicylic acid; Alb, to albumin; sal, to salicyl; the cross ×, to the quantity (grams) of feces voided; 'phthalein refers to phenolsulphonephthalein.

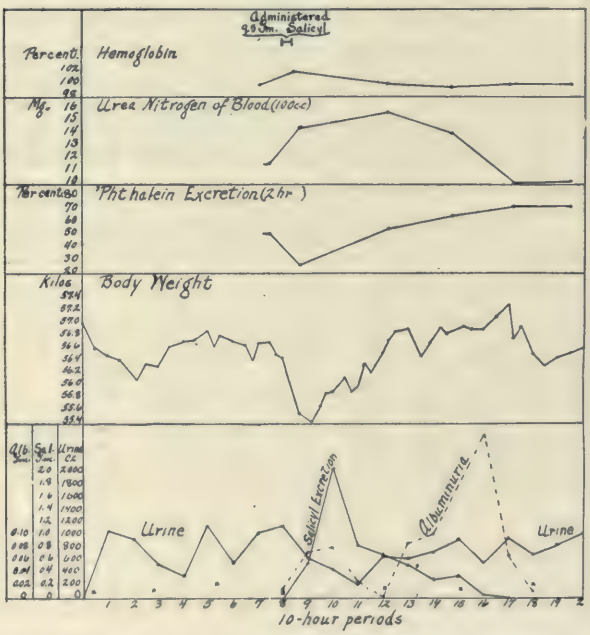

CHART 2.—Patient 23 (J. E.). Marked diaphoresis occurred from end of ninth to twelfth periods inclusive.

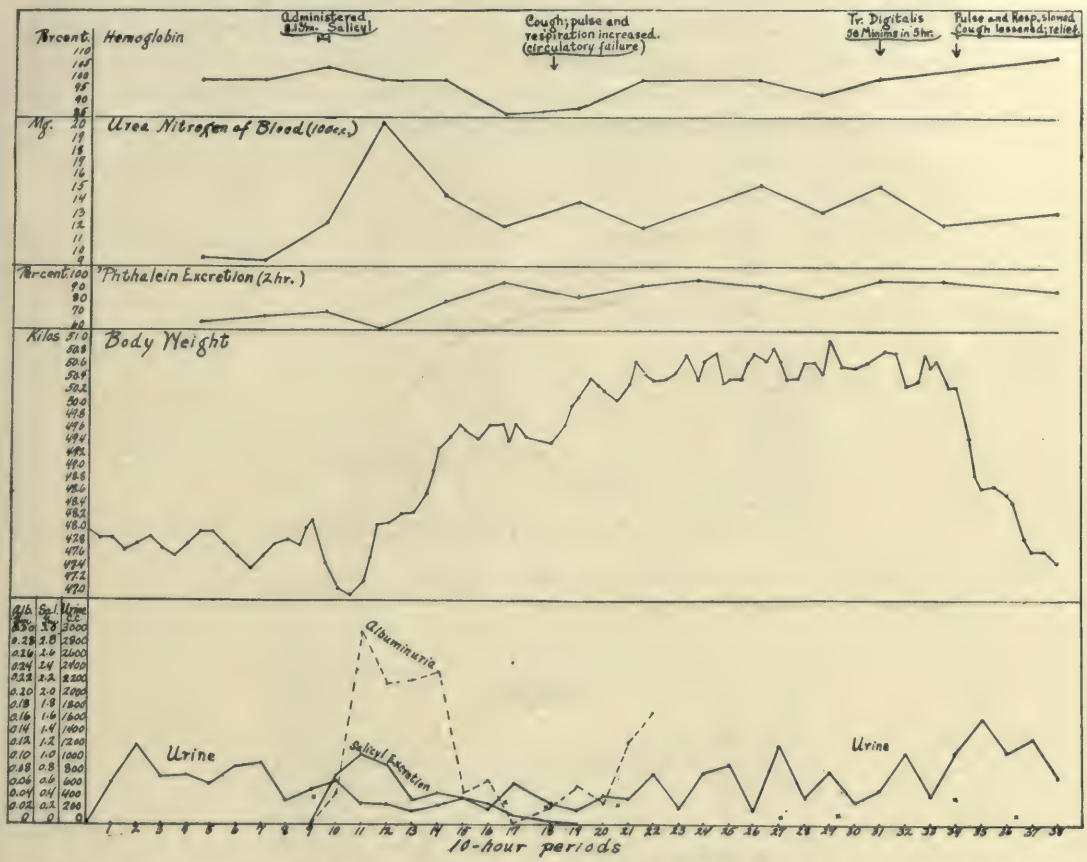

CHART 3.—Patient 24 (J. H.). Aside from the effects produced by the salicylate, this particular case presents an interesting study of digitalis action in circulatory embarrassment. About the time of appearance of certain objective symptoms, namely, increase in pulse rate, respiration and coughing, etc., there was demonstrable a dilution of the blood as indicated by a fall in the percentage of hemoglobin, a diminution in the urea content of the blood, an increase in body weight and a diminution in water output. Gradually the blood became more concentrated because the tissues now became the chief reservoir for the surplus fluid. This is indicated also by the persistence of the edema. Renal function became variable as indicated by the variable excretion of phenolsulphonephthalein and urea content of the blood, the albuminuria at the same time being markedly increased. In the meantime the only subjective symptom was a slight sensation of oppression in the chest. On inspection there was some slight fulness of the face, but otherwise edema was not demonstrable. These effects had now lasted for about 160 hours. The question arose as to whether the marked increase in body weight was due to improved nutrition, in part or whole, or anasarca resulting from circulatory embarrassment. This was tested out by the administration of tincture of digitalis, the result being a prompt and marked fall in body weight to the original level with a marked increase in urine output, improvement of renal function and some concentration of the blood. The various effects are strikingly shown in the curves of the chart. It was concluded, therefore, that the increase in body weight was due to anasarca as the result of circulatory embarrassment.

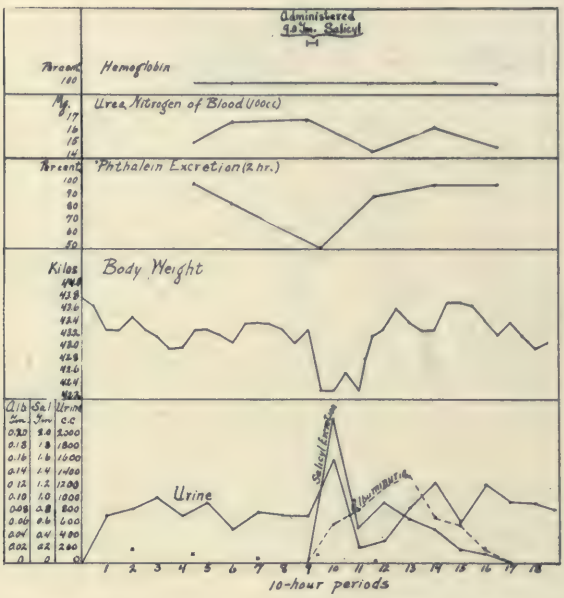

CHART 4.—Patient 25 (H. V.). Mild diaphoresis occurred from end of eleventh to thirteenth periods inclusive.

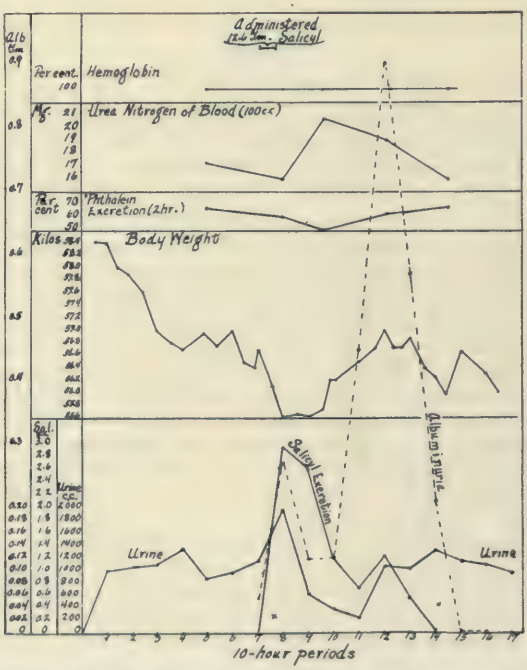

CHART 5.—Patient 26 (R. H.). Marked diaphoresis occurred from the ninth to end of eleventh periods inclusive.

nomena are concerned, these remained unchanged. In nearly every case there is evidence of a sharp decline in body weight about the time of toxicity. This is due, no doubt, to diaphoresis which occurs at this time and when the concentration of the drug in the tissues is at its maximum. This, of course, is a well known action of salicylate. Persistent sweating in those persons who habitually sweat considerably resulted in no modification of the curves of body weight. The loss of body weight cannot be attributed to increased urine or fecal output,

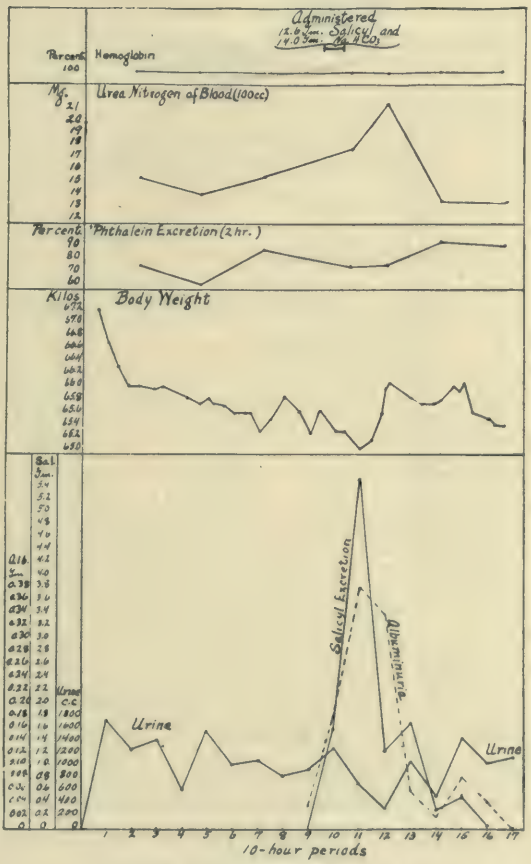

CHART 6.—Patient 27 (J. M.)

for these do not adequately compensate for the losses. The respiratory rate remained unchanged. The loss of water, therefore, could only have taken place by evaporation, that is, by diaphoresis.

It may be concluded that the administration of salicylate in full therapeutic doses causes a relative anuria, and this is due to retention of the water, that is, edema, as indicated by an increase in body weight unless modified by sweating.

2. *The Water Retention is not Due to Retention of Salicyl in the Tissues.*—This is indicated by the curves of salicyl excretion[4] in all the figures, which represent the data obtained for different individuals. It is seen that the maximum excretion of salicyl occurs at a time when the body weight begins to increase and when the water excretion is lowest. The excretion is at its minimum when the body weight is at its maximum; that is, when the water retention or edema is most marked, and in most individuals this was completed before the body weight reached its previous level. The excretion of salicyl does not

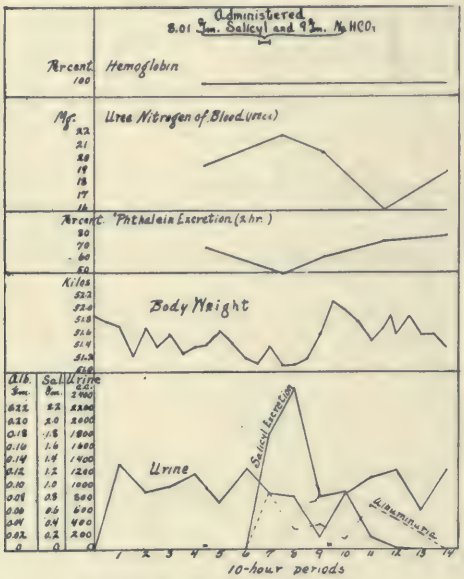

CHART 7.—Patient 28 (T. S.)

go parallel with the curve of body weight. There is no retention of salicyl and the retention of water, therefore, is not associated with or due to retention of salicyl in the tissues.

3. *The Water is not Retained by the Blood.*—This is indicated by the curves of hemoglobin percentage of the blood. Dilution of the blood was demonstrable in only one patient (24, Chart 3), in whom for a time there was some cardiac decompensation. On the other hand, an increase in the percentage of hemoglobin at toxicity was demonstrable in two patients. These persons sweated considerably from which it is inferred that there was some concentration of the blood at this time.

4. For other studies on the quantitative excretion of salicyl consult an earlier publication by Hanzlik, Scott and Thoburn: Jour. Pharmacol. and Exper. Therap., 1917, **9**, 247, and in connection with retention, Jour. Pharmacol. and Exper. Therap., 1917, **9**, 217.

In all other patients, whose blood was studied, no changes in blood volume were demonstrable.

From these evidences it appears logical to conclude that the water is retained in the tissues.

4. *The Retention is Chiefly of Renal Origin.* — Previous studies[5] on renal function showed that the administration of salicylate impairs the functional efficiency of the kidney. This also is the case in the

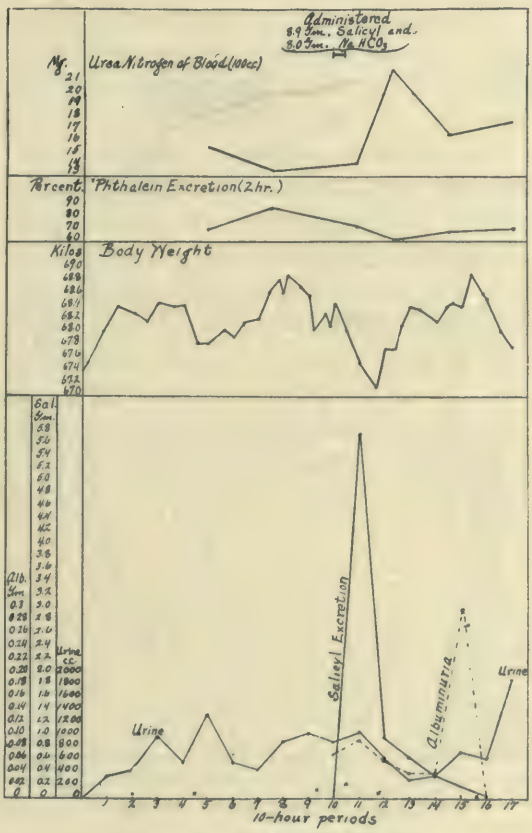

CHART 8.—Patient 29 (L. K.)

persons studied in connection with edema. Indeed it is one of the most constant features of the experiments, and is indicated in the various curves by a diminution in phenolsulphonephthalein excretion and at the same time an accumulation of urea nitrogen of the blood. Albumin, leukocytes and casts also appeared in the urines. This diminution in renal functional efficiency is demonstrable about the time of toxicity,

5. Hanzlik and Karsner: THE ARCHIVES INT. MED., 1917, **19,** 1016. Hanzlik, Scott and Thoburn: Ibid., 1030.

gradually becomes more severe, and finally (end of eighty to ninety hours) returns to its previous state. In almost every instance the impairment in renal function appeared before an increase in body weight was demonstrable. From this it seems that the renal factor plays an important rôle in the production of edema. It must be admitted that the part which tissues in general might play have not been absolutely excluded, for it is conceivable that in the beginning a marked diaphoresis could compensate for any accumulation of water.

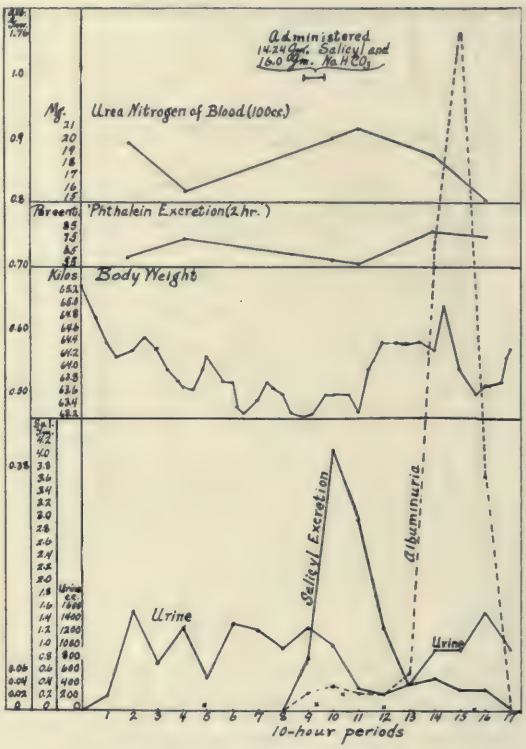

CHART 9.—Patient 30 (H. M.)

However, the following observation made by Sollmann and Pilcher[6] tends to exclude direct action on the tissues, or at least so far as local edema is concerned, and therefore lends support to the renal factor. In connection with the study of a series of agents which give rise to endermic reactions characterized by hyperemia, swelling (wheal formation), etc., the application of sodium salicylate to the abrazed skin does not give rise to local edema or urticaria such as is unmistakably produced by a large number of other drugs. The concentration used

6. Sollmann and Pilcher: Jour. Pharmacol. and Exper. Therap., 1917, **9**, 309.

by Sollmann and Pilcher is much higher than the concentration of salicyl we have found in the blood even after the largest doses used by us. There is no reason to believe that salicyl would be more effective in smaller than in larger concentrations.

5. *Effect of the Administration of Sodium Bicarbonate.* — If the edema produced by the administration of salicylate is of the same nature as the salt edema of Widal, it could conceivably be accentuated by the administration of such a salt as sodium bicarbonate. It has also been observed that the administration of large doses of bicarbonate can cause edema. This also gave us the opportunity to test the claim that is made by some, namely, that edema is due to the production of acid, and the rational therapy indicated consists of the administration of alkali.

Sodium bicarbonate together with salicylate was administered to Patients 27, 28, 29 and 30. The urines remained alkaline throughout the experiment, or at least, during the increase in body weight. The phenomena observed under the bicarbonate-salicylate medication as compared with salicylate alone, remained practically unaltered. Of four patients studied, only one (29, Chart 8) failed to show an increase in body weight, owing to marked diaphoresis.

Sodium bicarbonate, therefore, has no demonstrable influence on the edema and diminution in renal functional efficiency, albuminuria, anuria, etc., produced by the administration of full therapeutic doses of salicylate.

CONCLUSIONS

1. The anuria produced by the administration of full therapeutic doses of salicylate is due to retention of water as indicated by an increase in body weight unless modified by diaphoresis.

2. This retention is demonstrable about twenty hours after the start of administration of the salicylate and persists until the salicyl excretion is completed, that is, about eighty hours (three and one-third days).

3. The retention occurs chiefly in the tissues, for no dilution of the blood is demonstrable by estimations of hemoglobin.

4. The edema is accompanied by a diminution in phenolsulphonephthalein excretion together with an accumulation of urea nitrogen of the blood, and increased excretion of albumin, all of these elements reaching their previous levels with the disappearance of the edema.

5. There is, therefore, a diminution in renal functional efficiency, and since this generally makes its appearance before an actual increase in body weight is demonstrable (edema) and later coincides with it,

it seems that the renal factor plays an important rôle in the production of the edema.

6. These phenomena are not modified by the administration of sodium bicarbonate together with the salicylate, and in doses sufficient to maintain the urine alkaline.

We wish to express our thanks to Supt. C. H. McFarland and Dr. E. P. Carter, Chief of Medical Service, for extending the use of a special ward without which this and other investigations on salicylate would have been impossible; to Drs. Sheets and Kennedy, interns, and Messrs. T. W. Thoburn, M. E. Fulk and J. A. West of the third year class for various services rendered in connection with the work.

A STUDY OF POLIOMYELITIS

REPORT OF THE WORK OF THE MENINGITIS DIVISION OF THE RESEARCH LABORATORY IN THE 1916 EPIDEMIC *

JOSEPHINE B. NEAL, M.D., HARRY L. ABRAMSON, M.D.
AND ASSOCIATES
NEW YORK

Since the work of the meningitis division was somewhat varied during the epidemic of poliomyelitis, it is convenient to describe it under three heads: Clinical Work and Laboratory Work, Pathologic Studies and Research Work.

The meningitis division was established by Dr. Park in 1910, as a division of the Department of Preventive Medicine, to afford to the physicians of New York City expert assistance in the diagnosis and treatment of meningitis. In connection with this work, a great variety of meningeal conditions have been studied. Among these were about seventy cases of poliomyelitis before the epidemic, most of them being either nonparalytic, or at least seen before the paralysis had developed. This had given us very good training in the correlation of the clinical picture and the spinal fluid findings necessary for the differential diagnosis of nonparalytic cases of poliomyelitis.

Early in June, 1916, it was noted that several cases of poliomyelitis occurred in Brooklyn, and that they were rather closely grouped. June 9, a letter was written to the Department of Communicable Diseases calling attention to this fact.

PART I. CLINICAL AND LABORATORY WORK

JOSEPHINE B. NEAL, M.D., PHOEBE L. DU BOIS, M.D., HENRY W. JACKSON, M.D., CHARLES H. NAMMACK, M.D., CAROLINE ROSENBERG, M.D., AND SAMUEL PARNASS, M.D., WITH NATHAN NOVICK, HENRY W. ROGERS, HERMAN GERBER, HELEN JONES, MIRIAM RAPHAEL, ROSE RICHTER, LENA LEVINE AND DOROTHY COOPER
AS LABORATORY ASSISTANTS

Although effort has been made for a long time to differentiate poliomyelitis and establish it as a clinical entity, the first important con-

---

* Submitted for publication March 27, 1917.

* From the Department of Research, Bureau of Laboratories, Department of Health.

* The gold chlorid tests were carried out in Dr. George Draper's laboratory by Miss Georgia Cooper. We take pleasure in expressing our indebtedness to them for this valuable work.

* Preliminary report of the Quantitative Studies in Spinal Fluids was presented before the Society for Experimental Biology and Medicine, November, 1916. Compare Proc. Soc. Exper. Biol. and Med., 1916, **14**, 26.

tribution to the study was a monograph published by Heine[1] in 1840.

Colmer,[2] in 1843, published an account of an epidemic of ten cases occurring in West Feliciana in 1841.

Strümpell,[3] in 1884, published an article differentiating the cerebral type of the disease for the first time.

Medin,[4] in 1890, published a study, which, with Heine's, ranks as a classic. Indeed, poliomyelitis is often called Heine-Medin's disease, from the epoch-making work done by them. Medin's work was based on epidemics in Sweden.

The first considerable epidemic in the United States occurred in Otter Creek Valley, Vt., in 1894, and was reported by Dr. Charles Caverly. About ten small epidemics were reported in the United States during the next twelve years.

In 1905 the first great epidemic occurred, over 2,000 cases being reported in Norway and Sweden. This was carefully studied by Wickman,[5] whose work ranks in importance with that of Heine and Medin. He arranged an excellent classification, developed the epidemiology and pathology, demonstrated the contagious character of the disease, and described, for the first time, the nonparalytic or abortive form.

In 1907, a still larger epidemic, comprising about 3,000 cases, occurred in New York City.

In 1909, there was an outbreak of over 2,000 cases in Cuba.

In 1909 and 1910, epidemics appeared in various parts of the United States, District of Columbia, Iowa, Massachusetts, Minnesota, Indiana, Pennsylvania, Kansas, Maryland, New Hampshire, New York, Rhode Island, Virginia, Washington and Wisconsin: These varied in size from 200 to 500 cases, sometimes even more.

During this time important experimental studies, referred to elsewhere, were made both in this country and abroad.

A study of infantile paralysis in Massachusetts during 1910,[6] reprinted from the *Monthly Bulletin* of the State Board of Health in 1912, includes clinical, epidemiologic and experimental work.

---

1. Heine, Jacob: Beobachtungen über Lähmungszustände der untern Extremitäten und deren Behandlungen, Stuttgart, 1840; Spinale Kinderlähmung, Stuttgart, 1860.
2. Colmer: Am. Jour. Med. Sc., 1843, **5,** 248.
3. Strümpell: Jahrb. f. Kinderh., 1884, **22,** 173.
4. Medin: Verhandl. d. Xth internat. Med. Cong., 1890, **2,** 6 Abt., p. 37.
5. Wickman, Ivan: Beiträge zur Kenntnis der Heine-Medinschen Krankheit, Berlin, 1907; Die akute Poliomyelitis, oder Heine-Medinsche Krankheit, Berlin, 1911.
6. Infantile Paralysis in Massachusetts During 1910. Monthly Bull. Massachusetts State Board of Health, 1912.

An excellent monograph, by Peabody, Draper and Dochez,[7] in 1911, includes a careful clinical study, and also considerable laboratory and research work.

Kling and Leviditi[8] published, in 1913, a very interesting epidemiologic study of the spread of the disease on two small islands, Djursö and Yxnö, where the movements of the people could be very closely followed. The progress of the disease either by direct contact or through carriers, was clearly shown.

F. E. Batten[9] made a study of the epidemiology of the disease in England and gives in the Lumleian Lectures for 1916 a careful summary of the most important work done along various lines.

During the epidemic in New York in 1916, cases in which there was a disagreement between the department diagnosticians and the attending physicians were referred to us for diagnosis. This enabled us to study many atypical cases and to make some rather interesting differential diagnoses. From the middle of June until the middle of October, we were called on in 461 cases, in practically all of which poliomyelitis was suspected. Table 1 shows the final diagnoses, with a comparison of the patients seen and the diagnoses for the corresponding time in 1915.

TABLE 1.—Comparison of Diagnoses in 1915 and 1916

	June 15 to Oct. 15, 1916	June 15 to Oct. 15, 1915
Anterior poliomyelitis	312	7
Anterior poliomyelitis, doubtful	29	
Tuberculous meningitis	29	16
Epidemic cerebrospinal meningitis	18	11
Other purulent meningitides	8	5
Acute syphilitic meningitis	1	0
Meningism	18	8
Other diseases	46	18

The increase shown in the number of other meningeal conditions indicates that these cases are incorrectly diagnosed at ordinary times when recourse is not had so freely to lumbar puncture.

The classification of a disease so protean in its manifestations as poliomyelitis is unsatisfactory. Wickman's classification is compre-

7. Peabody, Draper and Dochez: A Clinical Study of Acute Poliomyelitis. Pub. Rockefeller Inst. for Med. Research, 1911.

8. Kling and Leviditi: Etudes sur la poliomyelitis Aigié Epidemique, Pub. de l'Inst. Pasteur, Paris, 1913.

9. Batten, F. E.: Acute Poliomyelitis (Lumleian Lectures, 1916), Brain, June, 1916, p. 115.

hensive, but is open to the objection that it is on both a clinical and a pathologic basis. It is also somewhat complex for general clinical use. It is as follows:

1. The spinal poliomyelitic form.
2. The form resembling Landry's paralysis.
3. The bulbar, or pontine.
4. The encephalitic.
5. The ataxic.
6. The polyneuritic (resembling neuritis).
7. The meningitic.
8. The abortive.

A classification on an anatomic basis and the degree of the lesion, is simple and quite easily used. We would suggest the following:

1. Nonparalytic Type.—Under this head are included cases in which the nerve cells are not sufficiently injured to produce paralysis. There may be weakness. Under this type should be classed meningitic cases and also those cases somewhat like tuberculous meningitis, but without motor disturbance, which we have called encephalitic, since the chief symptom seemed to be a depression of the sensorium. This is really only an accentuation of the drowsiness and stupor characteristic of the early stages. In these cases the motor cortical areas are not involved.

2. Ataxic Type.—The motor nerve cells are evidently not involved, but there is lack of coordination, ataxia, nystagmus, etc. In some cases an ataxic gait is the only sign of involvement of the central nervous system other than the sensory symptoms. The anatomic basis for this is proved by the postmortem findings of involvement of the cerebellum, Clark's column and the intervertebral ganglia. This type is very rare.

3. Type with Cortical Paralysis. — The upper motor neuron is affected, with resulting spastic paralysis. A true spastic paralysis is rare. More often are seen evidences of involvement of the upper motor neuron, increase of reflexes, or severe and prolonged convulsions. These convulsions are general and epileptic in character and may last for several hours.

4. Type with Spinal or Subcortical Paralysis.—The lower motor neuron is affected, with resulting flaccid paralysis. This is, of course, the most common form and the one first recognized and described.

Comparing this classification with that of Wickman, Group 4 corresponds with Wickman's Type 1, and includes his Types 2 and 3, since Type 2 is always an involvement of the lower motor neuron and Type 3 usually is. Group 3 corresponds with Wickman's Type 4, when actual lesions of the upper motor neuron are present; Group 2 with Type 5, Group 1 with Type 8, including those cases of Types 6

and 7 in which there is no paralysis, while cases of Types 6 and 7, in which paralysis is present, would fall under Group 3 or 4, depending on whether the upper or lower motor neuron is involved.

This classification is based on our experience during the epidemic, and cases were grouped under it after the epidemic was over. Had we been following it as the cases were studied, we could doubtless have made a more satisfactory grouping. Of course, cases sometimes fell in more than one group — Groups 2 and 4, most frequently.

The following is the classification of 512 cases:

Group 1	202	Mixed Groups:	
Group 2	4	Groups 2 and 4	3
Group 3	5	Groups 2 and 3	1
Group 4	296	Groups 3 and 4	1

Facial paralysis was rather common in this epidemic. Of 352 cases, there was facial paralysis alone in eighteen cases, combined with other paralysis in ten cases.

A manifestation of poliomyelitis, difficult to classify, is blindness. Wickman[5] says: "I may appropriately here mention that the optic nerve also is in rare cases affected." Tedeschi found complete blindness with optic atrophy in the left eye of a chronic case, and Wickman demonstrated optic neuritis in a recent case.

Three cases of blindness have been seen by the physicians of the meningitis division in poliomyelitis. In view of the rarity of the condition, a brief description of these cases may be of interest.

Case 1.—E. M., aged 3 years; illness began Sept. 23, 1911, with symptoms characteristic of poliomyelitis. Partial paralysis of left arm and left side of face occurred, with left internal strabismus. About 70 c.c. of clear cerebrospinal fluid were withdrawn October 14. The changes were characteristic of poliomyelitis: marked increase in cells, 98 per cent. mononuclears; bacteriology negative; albumin and globulin + +. October 24, the general condition was better but the child was blind. Early in November the sight began to improve, and by the middle of December the child was perfectly well.

Case 2.—I. C., aged 4 years 10 months. Illness began July 1, 1916, with paralysis of legs and neck and ptosis of left eyelid. The paralysis of the legs was spastic in type. Blindness developed. The patient died Sept. 11, 1916.

Case 3.—R. J., aged 1 year. Illness began Aug. 31, 1916, with symptoms characteristic of poliomyelitis. There was no paralysis, but the child was blind (as nearly as could be determined) for three days. It made a complete recovery.

It is generally accepted that the most common cause of death is respiratory failure, due to the progressive paralysis of the muscles of respiration. The question of death occurring as a result of respiratory failure, or of cardiac failure due to the respiratory or cardiac centers being involved, has received but little consideration. Wickman, referring to the occasional occurrence of Cheyne-Stokes respiration, says that it is undoubtedly due to the respiratory center being affected. He

also mentions the possibility of the involvement of the vagus. Realizing that this question lies to a great extent in the realm of speculation, certain observations point to the desirability of giving it serious consideration. It is certainly possible to conceive from the pathologic findings that this condition may exist. Cases occur in which the only lesions are in the bulb and pons, there being no involvement of the cervical regions of the cord where the nerves controlling the muscles of respiration take their origin.

During the epidemic, death occurred suddenly, without signs of cardiac failure, in a few cases in which there was no paralysis of the muscles of respiration. In one case death occurred without evidence of paralysis, evidently from cardiac disturbance. For twenty-four hours preceding death there had been intervals of great irregularity of the heart, though the heart itself, from the physical examination, was apparently normal. Such a condition might conceivably arise from a progressive involvement of the vagus center in the medulla.

In several instances there was evidence of a transient involvement of the cardiac or respiratory centers, as shown by marked irregularity of the heart or respiration, which cleared up completely. As a specific example of a fatal case of this kind, the following may be cited:

I. F., aged 2 years. The illness began July 26, 1916, with facial paralysis. The spinal fluid showed pathologic changes, such as are commonly found in poliomyelitis. Death occurred July 31, no signs of paralysis of the respiratory muscles having developed. The microscopic pathology of this case showed the lesions of poliomyelitis present only in the pons and bulb.

The classification of this particular type is difficult. Of course the lesions occur in the pons and bulb. These cases, especially when fatal, are usually associated with paralysis of the cranial nerves — the facial or glossopharyngeal, abducens, etc. These are lower motor neuron lesions and are classified by us under Group 4. We are at a loss to know how to place a lesion of the vital centers.

The existence of this type of lesion does not seem to have been very clearly differentiated in the past. Even Wickman refers to paralysis of the respiratory muscles and lesions of the respiratory center without clearly distinguishing the conditions. Doubtless further study will throw more light on the clinical and pathologic side of this question.

It is maintained by some authorities that poliomyelitis is essentially a general infection, and that symptoms of its effects on the central nervous system are entirely secondary in nature, when not absent altogether. It has even been suggested that paralytic cases may be in reality the atypical ones. Those holding this view would, in times of epidemics, diagnose as poliomyelitis cases presenting merely respiratory or gastro-intestinal symptoms, particularly if a case of frank

paralysis exists in the same family at the time. When we consider the prevalence of gastro-intestinal disturbances in children, more especially during the summer season, such a conclusion is hardly tenable, unless corroborated by characteristic findings in the spinal fluid.

Personal experience inclines us to believe that the changes in the spinal fluid commonly accepted as diagnostic of poliomyelitis do not exist independently of some definite clinical manifestation of involvement of the central nervous system. It does not seem possible that a disease accompanied by an inflammatory reaction in the central nervous system and meninges of sufficient severity to produce changes in the spinal fluid could fail at the same time to afford some clinical evidences of nerve involvement. Therefore, in the past, we have made it a rule to consider the possibility of poliomyelitis, and to perform lumbar puncture only in those cases presenting symptoms referable to the nervous system, such as hyperesthesia, Kernig's or the spinal sign, altered reflexes, stiffness of the neck, Macewen's sign, etc. In the absence of these signs and in the presence of a normal spinal fluid, we have always definitely excluded poliomyelitis.

When none of these signs was present we have usually considered a lumbar puncture unjustifiable. In the few cases in which we have performed it, the fluids have been normal.

During the recent epidemic we performed punctures irrespective of our own opinion as to the diagnosis, to clear up doubtful cases, and the results have justified our earlier views.

At the other extreme from those regarding poliomyelitis as a general infection and the paralytic cases as atypical, are physicians, few in number to be sure, who regard as suffering from poliomyelitis, only those patients with a frank paralysis. The following reasons seem to prove quite conclusively the existence of the nonparalytic type:

1. The filtered washings of the nose and throat of such patients, in a considerable number of instances, have produced typical poliomyelitis in monkeys.

2. The findings in the spinal fluid in these cases are identical with the findings in poliomyelitis with paralysis.

3. The findings in the spinal fluids in cases of meningism in gastro-enteritis, pneumonia, the exanthems, etc., are usually quite distinctly different.

4. The serum from nonparalytic patients possesses the same neutralizing power as the serum from paralyzed patients.

Symptoms of Onset.—The initial symptoms are much the same in all types of the disease, and they may be quite as severe in the nonparalytic as in the paralytic forms. There is a type of onset described

by Kling, Leviditi and others, which we have sometimes observed. In this, the disease is ushered in by somewhat indefinite symptoms of an intestinal or anginal nature. A remission of from one to several days then occurs, to be followed by a return of all symptoms, and usually by an accompanying paralysis.

While the onset may rarely be insidious, in the vast majority of cases it is very abrupt. Fever is probably the most constant, as well as usually the first, symptom. As a rule, it is high and of comparatively short duration, falling by crisis or by lysis. Next to fever, the most frequent symptom is a pronounced hyperesthesia or diffuse tenderness over the whole body. This is, perhaps, most marked in the legs and along the spine. There is also a decided drowsiness and the patient manifests great irritability when disturbed. Headache and vomiting are common. Constipation or diarrhea may be present; in our own experience, the former being more frequent. Retention of urine sometimes occurs, and this possibility should be constantly borne in mind. Convulsions, twitchings of groups of muscles, delirium, and pains in the neck, back, joints and limbs are other symptoms which may appear. Meningeal symptoms are pronounced in a fairly large portion of cases. These are, anteroposterior stiffness of the neck; Kernig's sign; Macewen's sign, or change in the percussion note over the lateral ventricles, due to distention with fluid. The reflexes may be exaggerated, but usually they are diminished or abolished. They are frequently unequal. The pupillary reflex is, as a rule, retained. Following these symptoms, paralysis may develop, most commonly appearing about the second day, though it may be delayed as late as the second week.

While occasional references to herpes zoster associated with poliomyelitis are noted in the literature, it would seem that the association must be accidental, or else especially characteristic of certain epidemics. In this epidemic no instances were seen by us of this manifestation, nor is there any record, to our knowledge, of herpes zoster occurring in experimental poliomyelitis. If it were due to the virus of poliomyelitis, it would seem that this manifestation would occur occasionally, at least, in monkeys artificially infected, inasmuch as in these cases the posterior root ganglia invariably show the typical pathologic lesions.

Differential Diagnosis. — In the first twenty-four to forty-eight hours after its onset, poliomyelitis must be differentiated from the early stages of epidemic meningitis, or mild purulent meningitis, and also from a meningism accompanying pneumonia or other infection. The clinical pictures presented by the diseases mentioned are quite similar, and it is in distinguishing between them that the examination of the spinal fluid affords us the most reliable information.

When seen a week or more after onset, cases of poliomyelitis, especially if presenting cerebral symptoms, must be distinguished from tuberculous meningitis.

Though the differential diagnosis of typical cases of early poliomyelitis and early purulent meningitis would be fairly easy, many cases are atypical.

While epidemics of poliomyelitis usually occur in hot weather, and epidemics of meningitis in the winter or spring, sporadic cases of either occur at any time.

A history of a gastro-enteritis or an anginal attack three or four days prior to the onset, is much more suggestive of poliomyelitis than of meningitis. A history of an otitis media, an operation on the nose or throat, or a severe injury to the head with possible fracture of the skull, makes one suspect a meningitis, due most likely to the pneumococcus or streptococcus.

The temperature in poliomyelitis is usually higher at the onset, but falls more quickly than in meningitis.

There is usually greater hyperesthesia in poliomyelitis; the reflexes are more likely to be unequal and the pupillary reflexes are very seldom lost.

In meningitis there is usually greater stiffness of the neck and a more pronounced Kernig. Delirium is far more common than in poliomyelitis. A hemorrhagic eruption, or herpes, if present, strongly suggests meningitis.

The differential diagnosis between poliomyelitis and meningism is much more difficult until the underlying cause of the meningism develops. Even then we may wonder if the pneumonia or gastro-enteritis, etc., may not be a complication of the poliomyelitis.

In differentiating poliomyelitis and tuberculous meningitis, one should remember that while the onset is usually sudden in poliomyelitis and gradual in tuberculous meningitis, some few cases of poliomyelitis give a history of a gradual onset, and occasionally tuberculous meningitis begins abruptly. In the cases of poliomyelitis resembling tuberculous meningitis, the stupor is usually not so profound, there is no projectile vomiting, the pulse is usually regular, and the progress of the case after the first week or ten days is generally toward recovery.

Occasionally in tuberculous meningitis a paralysis develops of the muscles of the eye. Sometimes other paralyses develop, as of the face or arms. These are usually transitory.

In all these conditions the differential diagnosis depends greatly on the spinal fluid findings.

An attempt was made to follow up cases to determine how infectious poliomyelitis is, or how much natural immunity children have, by

studying the number of secondary cases developing in families, a member of which was known to have the disease.

In following up 360 cases it was found that in 198 instances there were other children in the family who were, therefore, directly exposed to the disease. The children thus directly exposed numbered 443 and of these twenty-eight, or 6.3 per cent., developed the disease. This is in accordance with work done by Emerson[10] in Massachusetts and Hill[10] in Minnesota, in 1909. The distribution by families was as shown in Table 2.

TABLE 2.—Occurrence in Contacts in Same Family

Number of Children in Family	Number of Families	Children Developing Disease	Number of Children in Family	Number of Families	Children Developing Disease
2	72	13	6	9	1
3*	60*	9*	7	5	1
4	31	4	8	1	0
5	18	0			

* Among these families in two instances all three children developed the disease. These were the only instances in which more than two children were sick.

Table 2 shows that a relatively large number of children must have a considerable natural immunity to the disease, since, when exposed so closely to poliomyelitis, so few developed it.

Outcome of Cases.—The results at the end of two months in 507 cases studied were as follows:

Class 1 (Nonparalytic): Of 202 cases, 173 recovered completely; 29 had weakness remaining.

Class 2 (Ataxic): Of 4 cases, 4 patients recovered.

Class 3 (Cortical or upper motor neuron paralysis): Of 5 cases, 5 patients died.

Class 4 (Spinal or lower motor neuron paralysis): Of 296 cases, 32 recovered completely; 32 recovered with weakness; 130 had paralysis remaining after two months; 102 died.

The cases under Classes 2 and 3, of course, are too few to make it possible to draw conclusions.

It will be noticed that of these 507 cases, 202, or 40 per cent., were nonparalytic. We saw a relatively large proportion of nonparalytic cases, since that type of case was the one in which there was most frequently a difference of opinion, and which we were therefore called to see.

10. Infantile Paralysis in Massachusetts in 1909. Bulletin Massachusetts State Board of Health, 1909.

Of Class 4, the spinal or lower motor neuron type, 130, or 67 per cent. of the 194 surviving, showed a residual paralysis at the end of two months.

Treatment.—In the minds of the general public, and of most physicians, there exists a close analogy between the use of serum in epidemic meningitis and in poliomyelitis, and its success in the former has influenced them to have faith in its success in the latter. The pathology of the two conditions, however, is quite different. In acute purulent meningitis the process is limited almost entirely to the meninges, the brain and cord substance being little, if at all, involved, though there may be some secondary congestion. In poliomyelitis, however, the pathologic picture is reversed. Here, the brain and cord substance is mainly involved, whereas the inflammation in the meninges is secondary. Injecting a foreign substance into the slightly inflamed meninges sets up, in most cases, an acute aseptic meningitis, as is shown by changes in the spinal fluid, and clinically, by the increased temperature, rigidity of the neck and other signs of meningeal irritation. It is possible that this increased inflammatory reaction may tend to accentuate indirectly the inflammatory changes already existing in the subjacent substance of the brain and cord. That this reaction may be harmful is borne out by the results of animal experimentation, which are described in another place. On the other hand, certain workers feel that a beneficial phagocytosis may result from the increased leukocytes. In meningitis, however, the injection of serum into actively inflamed meninges is not followed by an increase in the inflammatory reaction, as is evidenced by the clearing up of the fluid and the amelioration of the clinical symptoms in favorable cases.

It seems to us, therefore, that the setting up of an acute aseptic meningitis may be harmful. As to its specific neutralizing power, this would have to be exerted very speedily, since the damage is so often done within forty-eight to seventy-two hours after the onset of symptoms. Such a speedy effect is not seen in the case of antimeningitis serum, tetanus antitoxin, etc.

The unanimous opinion of the physicians of the meningitis division is voiced in the preceding discussion.

The members of the meningitis division did not administer serum in a very large number of cases, because the early experiences were so discouraging that they did not feel that they could urge its administration. The reaction following the introduction in the cases of the patients who survived was often so severe that it was felt that it might have been an injurious factor in some instances.

They feel that the best results of treatment in early cases is obtained by complete rest, with lumbar puncture for the relief of signs of men-

ingeal irritation. Symptomatic and hygienic treatment should, of course, be carried out. The importance of rest cannot be too strongly emphasized. That form of treatment would need to be of definite and well-established value that can justify the frequent disturbance of a desperately sick child for the administration of treatment intraspinally.

THE CEREBROSPINAL FLUID IN POLIOMYELITIS

In 1908, Dr. Martha Wollstein[11] published a biologic study of the cerebrospinal fluid in anterior poliomyelitis. This included bacteriologic and complement fixation work, rather than cytologic and chemical studies, and refers in detail to still earlier work along those lines.

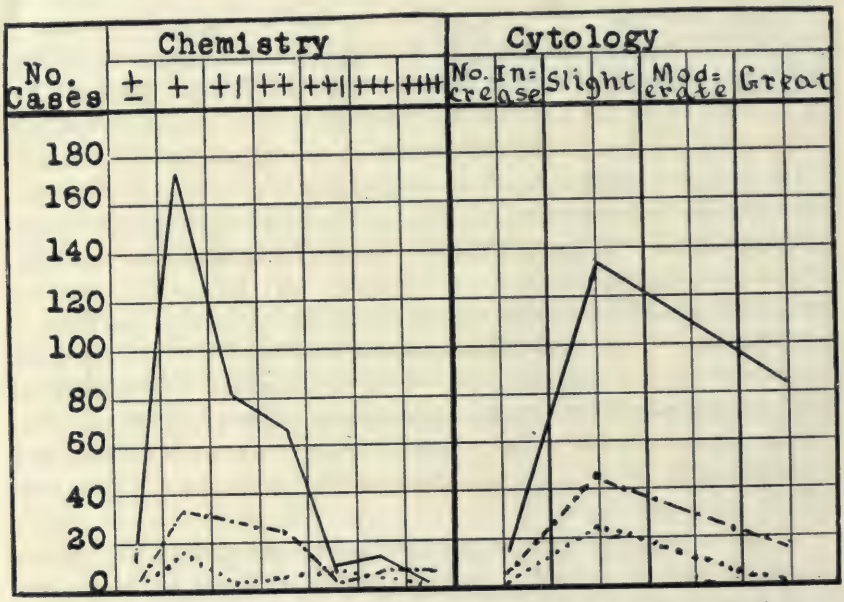

CHART 1.—Showing the variations in the chemistry and cytology of the cerebrospinal fluid in poliomyelitis. Upper curve ————————, first week; middle curve —.—.—.—.—.—., second week; lower curve ....., subsequent weeks. An idea may be gained from these curves as to the significance of the laboratory findings in the first and second and subsequent weeks. In the cytology the curves are nearly parallel, showing no tendency for greater cytology at any one time than another. There were relatively more cases with low chemical findings in the first week than in the later periods, but low chemical findings predominated in all three periods.

Gay and Lucas,[12] in 1910, published one of the earliest and most important studies, embracing cytologic and chemical work on the spinal fluid, both from human cases and from the experimental disease in monkeys.

11. Wollstein: Jour. Exper. Med., 1908, **10,** 476.
12. Gay and Lucas: THE ARCHIVES INT. MED., 1910, **6,** 330.

The spinal fluid was carefully studied in the monograph published by Peabody, Draper and Dochez,[7] already referred to, and this work was continued by Fraser.[13]

PART II. PATHOLOGIC STUDIES

HARRY L. ABRAMSON, M.D.

The routine laboratory work consisted in the examination of spinal fluids, including those withdrawn by the personnel of the meningitis division, those sent in by private physicians, and those withdrawn at the Willard Parker Hospital and at the Kingston Avenue Hospital. To take care of the fluids at the latter place, it was necessary to establish a laboratory there.

The examination of the spinal fluid is the most valuable laboratory aid in the diagnosis of poliomyelitis, but even here there are no pathognomonic findings, as, for example, the infecting organism in a purulent or a tuberculous meningitis. It is by ruling out other conditions that it is of value, and it is of the greatest service only when correlated with a careful clinical study of the case.

The spinal fluid in poliomyelitis is usually increased in amount and escapes under pressure. It is clear or slightly hazy in appearance, and sometimes shows the fibrin web formation which was formerly considered pathognomonic of tuberculous meningitis.

In poliomyelitis, the spinal fluid shows evidence of an inflammatory reaction — there is a varying increase in the cells and in the albumin and globulin. In a few cases these evidences of an inflammatory reaction are well marked; in most cases they are moderate; while in a few cases, at the other extreme, they are so slight and the fluid so nearly approaches normal that it is difficult to make a definite statement in regard to the findings. The reduction of Fehling's solution in these fluids is practically always as prompt as in normal fluids.

The technic which we employ in examining spinal fluids is as follows:

Technic.—All clear or slightly cloudy fluids in approximately the same amounts are centrifuged for an hour at high speed. From the sediment spreads are made, taking care to use as nearly as possible, the same area on the different slides. The sediments of clear fluids are stained by the Ziehl-Nielsen method for the tubercle bacillus; the sediments of slightly cloudy fluids for both the tubercle bacillus and by the Gram method. From this stained sediment we can estimate the increase in cells as slight, moderate, great, or very great. We do not feel that the exact number of cells has more than an academic interest. Indeed, as the cell count was the first study to be made in spinal fluids, an undue emphasis has been placed in the past on finding out the presumably exact number of cells, and many workers having made this deter-

13. Fraser, F. R.: A Study of the Cerebrospinal Fluid in Acute Poliomyelitis. Jour. Exper. Med., 1913, **18,** 242.

mination, have been content to rest on it, omitting other investigations at least equally important. Moreover, the attempt to determine the exact number of cells in the spinal fluid, even in the hands of experienced laboratory workers, is not so simple or accurate a problem as doing a white cell count in the blood. This was borne out by our experience during the summer, when the same fluid examined under the same conditions by different workers gave widely varying results. This is to be accounted for by the presence of a few red blood cells that are often found, even in the clearest fluids. It is difficult to get rid of these red blood cells, as only a small amount of diluting fluid can be used. Detritus also may be mistaken for cells.

Certain of our workers who have had experience with both methods have become convinced that, on the whole, the smear method is the more reliable. A fixed and stained preparation leaves no doubt as to the exact character of sediment. We made a fair number of cell counts in connection with the smear method, and we find that, on the whole, the two methods check up very well. Indeed, there were several striking instances of the greater reliability of the smear method.

The cell count in poliomyelitis and tuberculous meningitis, while on the average higher in the latter, overlaps for so wide a range as to render the differential diagnosis by this point most unreliable. Moreover, while some claims to the contrary have been made, it is not our experience that the number of cells in poliomyelitis fluids bears any relation to the prognosis of the case, as is shown in Tables 5 and 6. From these stained sediments we also estimate the percentage of mononuclears and polymorphonuclears, and note the presence of endothelioid and polyform cells. The presence or absence of bacteria was also noted. Cultures were made from all specimens. In the case of uncontaminated poliomyelitis fluids they have been uniformly negative.

The chemical tests that we use are the nitric acid ring test for albumin, and the Noguchi butyric acid test for globulin. The albumin and globulin practically always run parallel, but they serve as a check on each other. The small amount of albumin and globulin present in normal fluids is marked ±. The signs +, +1, ++, ++1, +++, ++++, represent increasing amounts and serve as a rough quantitative estimation. The presence of glucose is tested by using an equal amount of Fehling's solution and spinal fluid, and it is marked with regard to the speed and the amount of reduction as —, +, +1, ++, +++. The globulin reaction and the reduction of Fehling's solution should not be read for at least half an hour.

Findings.—Taking up these points somewhat in detail, let us first consider the cytology. The increase in cells varies very greatly, both in different cases and in the stage at which the puncture is done. Our counts have varied from slightly above normal, 15 or 20, to 1,200. The counts tend to fall off after the first week, and by the end of the second week have usually fallen nearly to normal. That this does not always happen is shown in Table 1.

The cells usually show a preponderance of mononuclears, but in a few instances there is over 50 per cent. of polymorphonuclears. It has been stated that early in the disease there is an excess of polymorphonuclears, which later is replaced by mononuclears. A large number of early fluids, on the second, third and fourth days, were examined by us. Out of a series of 2,000 fluids, many of them early, the polymorphonuclears predominated in only thirty-nine cases as follows: 4 on the second day; 6 on the third day; 1 on the fourth day; 5 on the fifth day;

3 on the sixth day; 7 on the seventh day and so on as late as the twenty-first and twenty-seventh days. We feel, therefore, that the polymorphonuclears represent a special type of reaction — not a stage of the disease. Often, even in fresh fluids, the cells are so degenerated that it is difficult to classify them. There are large mononuclear cells, endothelioid in type, that seem to us to occur more frequently in poliomyelitis than in other conditions. The so-called polyform cells are also found.

The albumin and globulin are usually slightly to moderately increased.

Fehling's solution, as has been stated before, is practically always well reduced. The fluids that show a poorer reduction are usually those with the larger amount of albumin and globulin.

Differential Diagnosis of Poliomyelitis Fluids.—The slightly cloudy fluids must be differentiated from those of early cases of purulent meningitis and from the slightly cloudy fluid that occasionally occurs in tuberculous meningitis. The clear, or practically clear, fluids must be differentiated from rare, early cases of purulent meningitis, tuberculous meningitis, syphilis of the central nervous system, especially acute syphilitic meningitis, and meningism. Other rarer conditions might be mentioned, but these are the most important.

In early cases of purulent meningitis the spinal fluid shows a varying degree of cloudiness, except in very rare instances, when it may be clear. A greater increase in albumin and globulin is usually found than occurs in poliomyelitis, with a poorer reduction of Fehling's solution. The cells in the fluids of purulent meningitis are 90 per cent. or more polymorphonuclears, and the etiologic organism is always found except in the mildest cases, or in cases of basilar meningitis when the puncture is done late. In certain mild cases of meningitis — probably of the epidemic variety — the meningococci may never be positively demonstrated in the fluid. In purulent meningitis, due to other organisms, these practically always appear later. In two instances we have seen clear fluids from early cases of epidemic meningitis of about eighteen hours' standing. Although the cellular reaction was so slight, the meningococcus was demonstrated to be present in the fluid by smear and culture.

The fluid in tuberculous meningitis most nearly resembles that of poliomyelitis. It is practically always clear, with a cellular increase consisting largely of mononuclears, though in very acute cases it may be distinctly cloudy, with an excess of polymorphonuclears. Fortunately, in these cases, the tubercle bacillus is usually easy to demonstrate. The number of cells per cubic millimeter is usually greater than in poliomyelitis; the increase in albumin and globulin is more marked, and the reduction of Fehling's solution is not so good.

TABLE 3.—Relation of Day of Puncture to Laboratory Findings

Day of Puncture	Cytology					Chemistry						
	No. of Fluids	No Increase	Slight	Moderate	Great	±	+	+1	++	++1	+++	++++
1	2	...	1	...	1	..	1	1				
2	52	2	22	17	11	2	30	13	3	2	1	1
3	63	2	20	21	20	3	29	14	13	1	2	1
4	71	4	29	22	16	2	37	17	9	1	5	
5	77	3	24	30	20	2	34	14	20	4	2	1
6	50	3	25	11	11	1	28	11	8	..	2	
7	39	2	16	13	8	1	16	12	7	1	2	
8	27	...	12	8	7	1	10	5	6	1	4	
9	20	...	8	8	4	1	12	4	2	1		
10	15	2	7	6	..	1	3	4	4	..	..	3
11	9	1	3	2	3	..	1	5	2	..	1	
12	15	...	10	3	2	1	5	3	1	1	3	1
13	11	1	4	4	2	1	3	1	3	1	2	
14	6	1	3	1	1	..	..	2	2	2		
15	5	...	3	2	..	..	1	1	3			
16	2	...	2	...	..	..	..	..	1	..	..	1
17	5	...	5	...	..	..	4	..	1			
18	1	...	...	1	..	..	..	..	..	1		
19	2	...	1	1	..	..	1	..	1			
20	2	...	2	...	..	..	1	..	..	1		
21	6	...	2	3	1	..	2	1	2	1		
23	1	...	...	1	..	..	..	1				
24	1	...	1	...	..	1						
25	1	...	1	...	..	..	..	1				
27	1	...	1	...	..	..	1					
28	1	...	1	...	..	..	..	1				
30	4	...	2	1	1	..	1	2	..	1		
35	3	2	1	...	..	..	1	..	1	1		
40	2	...	1	1	..	..	2					
41	1	...	1	...	..	..	..	..	..	1		
43	1	...	1	...	..	..	1					
48	1	...	...	1	..	..	1					
50	3	...	2	1	..	..	2	1				
	500	23	211	158	108	17	227	114	89	21	24	8

The great majority of cases show a slight or moderate increase in the cells and a + or +1 chemistry. The pathologic changes in the fluid both as to cytology and chemistry persist longer than has commonly been believed.

In rare instances, when clinical signs are confusing and when the results of the cellular examination and chemical analysis are indefinite, and it is impossible to demonstrate the tubercle bacillus in the fluid, a positive diagnosis must wait on the results of animal inoculation.

The fluid of an acute syphilitic meningitis closely resembles the fluid of poliomyelitis, and the clinical signs are also confusing. The Wassermann reaction is the best method of differentiating the two conditions. Of course, a positive Wassermann would not rule out poliomyelitis in an old syphilitic condition, but this, combined with the clinical conditions and the progress of the case, makes one reasonably sure of the diagnosis. It was suggested at first that the products of degeneration present in the spinal fluid of poliomyelitis cases might give a nonspecific Wassermann reaction. Tests in about 350 cases were made by Miss May Wilson, and have indicated that this is not true.

TABLE 4.—Relation of Cytology to Chemical Findings

Cytology		Albumin and Globulin						
		±	+	+1	++	++1	+++	++++
No increase	28	1	12	7	8	0	0	0
Slight	211	9	105	59	35	9	11	3
Moderate	158	5	73	35	31	5	6	3
Great	103	2	37	33	20	7	7	2
	500	17	227	114	89	21	24	8

The chemistry does not run parallel with the cytology, as is clearly shown in the table.

TABLE 5.—Relation of Condition at the Time of Puncture to Findings

		Cytology				Chemistry						
		No Increase	Slight	Moderate	Great	±	+	+1	++	++1	+++	++++
No paralysis	41	5	15	15	6	2	26	6	3	1	1	2
With weakness	261	11	102	83	65	12	121	54	50	13	8	3
With paralysis	198	7	94	60	37	3	80	54	36	7	15	3
	500	23	211	158	108	17	227	114	89	21	24	8

A majority of cases had slight increase in cells. A majority of cases had one plus chemistry. There is no relation between the paralytic condition and the spinal fluid findings, either as regards cytology or chemistry.

The fluid of meningism is clear, increased in amount, and practically always normal in character. The few exceptions to this that we have found in a large number of cases have fallen mainly into three groups — fluids from patients with prolonged and severe convulsions; fluids in severe whooping cough, and fluids removed just prior to death. In these cases there have sometimes occurred an increase in cells, or in albumin and globulin, or in both. In convulsions, there is probably edema, in whooping cough minute hemorrhages, and, just before death, circulatory changes, to account for it.

Lange's colloidal gold test has been used to some extent by workers to whom we have given specimens of fluid. This is discussed later.

Two rare types of spinal fluids sometimes occur in poliomyelitis when the hemorrhagic process has been more than usually severe. The first of these is of true hemorrhagic character, the red blood cells being evenly diffused throughout the fluid. When collected in successive tubes, the specimens are all homogeneous, showing no change in the

TABLE 6.—Relation of Cell Increase to Outcome; Condition After Approximately Eight Weeks

		Cytology		Complete Recovery	Weakness or Recovering Paralysis	Paralyzed	Dead	Mortality Per Cent.
Lumbar puncture in first week of illness	354	No increase	16	9	0	4	3	19
		Slight	137	57	20	34	26	19
		Moderate	114	50	10	25	29	25
		Great	87	35	11	23	18	20
Second week	103	No increase	5	0	1	2	2	40
		Slight	47	18	9	15	5	10
		Moderate	32	15	2	4	11	34
		Great	19	7	4	5	3	16
After second week	43	No increase	2	1	1	0	0	0
		Slight	27	10	1	12	4	15
		Moderate	12	3	2	6	1	8
		Great	2	2	0	0	0	0
	500		500	207	61	130	102	

In the first and second weeks the cases with a moderate increase (from about seventy-five cells to 150 cells) had a higher mortality than the cases with a slight increase, or the cases with a great increase. It would be safe to conclude from this that a high cell count does not carry with it a bad prognosis.

intensity of the hemorrhage. This serves to differentiate the fluid from bloody fluids obtained by the accidental puncture of a vein.

Evidence of an older hemorrhage occurs in the second of these rarer fluids, which, having a characteristic yellow color and coagulating spontaneously, illustrates the so-called syndrome of Froin. These fluids occur in other conditions, and are, therefore, not pathognomonic of poliomyelitis.

While about 2,000 poliomyelitis fluids were examined, only 500 were carefully studied. Five hundred is accepted by statisticians as a number furnishing absolutely reliable data from which to draw conclusions It seemed better, therefore, to take this number and make careful studies, combining clinical data with the spinal fluid findings, rather than to try to use a larger number and study the data less thoroughly.

TABLE 7.—Relation of Chemistry to Outcome

		Chemistry	Complete Recovery	Weakness	Paralyzed	Died	Mortality, per Cent.
First week	354	+	6	1	1	3	27
		+	91	18	37	29	16
		+1	27	14	21	20	24
		++	19	6	20	15	25
		++1	1	1	4	3	33
		+++	2	1	6	3	35
		++++	1	1	0	1	33
			147	42	89	76	
Second week	103	±	4	0	0	1	20
		+	13	5	7	9	26
		+1	6	4	8	6	25
		++	9	4	5	2	10
		++1	3	0	3	0	0
		+++	3	1	3	3	30
		++++	2	0	0	2	50
			40	14	26	23	
Third week	43	±	0	0	0	1	100
		+	9	1	7	1	5½
		+1	2	2	4	0	0
		++	6	2	1	0	0
		++1	3	0	2	1	16
		+++	0	0	0	0	0
		++++	0	0	1	0	0
			20	5	15	3	
	500		207	61	130	102	

Of course with the smaller numbers, the mortality percentage means practically nothing. In the first week, cases with a + chemistry did better than those with a higher chemistry, but this did not hold in the second week. It would seem safe to conclude from this that the chemistry has no very definite prognostic value.

TABLE 8.—Relation of Condition at Time of Puncture to Outcome; Condition After Approximately Eight Weeks

Lumbar Puncture in		Condition at Time of Puncture		Complete Recovery	Weakness or Recovering Paralysis	Paralysis	Dead
First week of illness.....	354	No signs of paralysis.....	31	25	2	1	3
		Weakness or other marked symptoms....	197	108	25	30	34
		Paralyzed in some part.....	126	18	14	55	39
Second week...	108	No signs.....	8	6	1	1	0
		Weakness.....	48	28	8	7	5
		Paralyzed.....	47	6	7	18	16
After second week.....	43	No signs.....	2	2	0	0	0
		Weakness.....	16	11	1	1	3
		Paralyzed.....	25	3	3	17	2
	500		500	207	61	130	102

This table shows that while, after the first week, as is obvious, the chances of recovery are better, nevertheless, even later, it is quite impossible to make a prognosis that is at all definite.

PART III. RESEARCH WORK

1. GOLD CHLORID TEST.

J. B. Neal, M.D., and H. Jones

Zsigmondy, following an exhaustive study of the subject of the "coagulating" action of electrolytes on metallic colloidal solutions, was able to find a definite measure of the protective action of certain colloids, especially proteins, on the precipitation of gold suspensions by sodium chlorid. The degree of protection was specific for each protein he examined.

By using this general method he was unable to distinguish between syphilitic and normal serums.

Lange proceeded further and found that normal spinal fluids, suitably diluted with a 0.4 per cent. solution of sodium chlorid, cause no alkalination in suitable solutions of colloidal gold, and abnormal spinal fluids cause partial or complete precipitation of colloidal gold, with resultant color changes occurring in curves, which tend to be almost specific for certain diseases, particularly those of syphilitic origin.

This specificity is characterized by maximal color changes within dilution zones.

TABLE 9.—Summary of 500 Cases

Types of Cases		Cytology				Chemistry							Outcome			
		No Increase	Slight	Moderate	Great	±	+	+1	++	++1	+++	++++	Complete Recovery	Weak	Paralyzed	Died
Class 1 No paralysis.....	202	12	77	65	46	12	103	36	35	8	5	3	173	29		
Class 4 Flaccid paralysis.....	296	11	133	92	62	5	123	77	54	13	19	5	32	32	130	102
Class 2 Ataxic.....	2	...	1	1	...	....	1	1	....	....	....	....	2			
	500	23	211	158	108	17	227	114	89	21	24	8	207	61	130	102

The cases were about evenly divided between two types—paralytic and nonparalytic.

Both types in the majority of cases had slight increase and one plus chemistry.

The paralyzed type in the majority of cases remained paralyzed.

The nonparalyzed type in the majority of cases recovered.

Out of 500 cases, in most there was a slight to moderate increase; in most there was one and one and one-half chemistry; in most there was recovery.

The percentage of those that made complete recovery after being paralyzed is 12.2.

The complete recovery among those not paralyzed is 76.2 per cent.

Fluids from different types of meningitis give reactions with greatest intensity in higher dilutions.

Paretic fluids cause complete flocculation in the first four to six dilutions.

Tabes and cerebrospinal lues give maximal reactions in fourth to fifth dilutions.

We have Lange results on 114 poliomyelitis fluids (Table 10).

Colloidal Gold Test.—Into the first of eleven test tubes put 0.9 c.c. of fresh, sterile 0.4 per cent. sodium chlorid solution. Into each of the remaining tubes put 0.5 c.c. of the 0.4 per cent. sodium chlorid solution. Add to the first tube 0.1 c.c. of the spinal fluid to be tested. Mix well.

Transfer 0.5 c.c. of the resultant 1 to 10 dilution of spinal fluid to the second tube. Mix well.

Transfer 0.5 c.c. of the resultant 1 to 20 dilution of spinal fluid to the third tube. Mix well.

Proceed in this manner up to and including the eleventh tube.

By this method a series of dilutions of spinal fluid is secured, in geometrical progression, ranging from 1 to 10, to 1 to 5,120.

Now add to each tube 2.5 c.c. of colloidal gold solution.

Shake each tube thoroughly and do not read for twelve hours.

The various types of color changes seen in a positive gold reaction are indicated by numerals as follows:

Complete decolorization	5	Lilac or purple	2
Pale blue	4	Red-blue	1
Blue	3	Brilliant red-orange	0

A normal fluid would remain brilliant red-orange color and would, therefore, read 00000000000 or 1110000000.

A poliomyelitis fluid would remain brilliant red-orange color in the first two tubes, slightly bluish in the third, purple in the fourth tube, and again bluish in the fifth, returning to normal red-orange in the sixth tube, and would, therefore, read 00123000000 — being a weak syphilitic curve.

A meningitis fluid unchanged in the first two tubes and ranging from this to colorless in the ninth tube and back to original in the eleventh tube, would read 00011245210.

Charts showing these typical reactions and readings are appended.[14]

Chart 2 shows the three curves of paretic, meningitic and syphilitic spinal fluids, according to the Bulletin of the Johns Hopkins Hospital, referred to.

Charts 3 to 8 show various poliomyelitis curves of fluids of our own.

Chart 9 is the composite of 3 to 8, giving the average curve for 114 fluids.

Our own fluids fell into six different groups, depending roughly on the albumin and globulin content. These are shown in Charts 3 to 8, while Chart 9 is a composite.

14. These charts are taken from Bull. 298, Johns Hopkins Hosp., 1915, **26.**

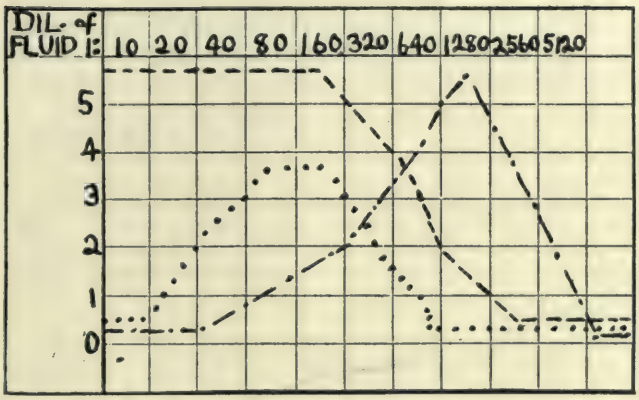

CHART 2.—Curves of cases of paretic, meningitic and syphilitic spinal fluids, reported in Bulletin Johns Hopkins Hospital, 1915, **26,** 298. Dilution of fluids in each instance as shown in figures at the top of the chart, 1 : 10, etc. Paretic, 5555531000; syphilitic, 0123321000; meningitic, 00011245210.

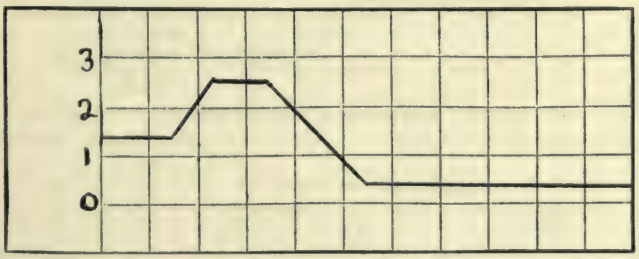

CHART 3.—Curve in forty of our poliomyelitic fluids: 1122100000.

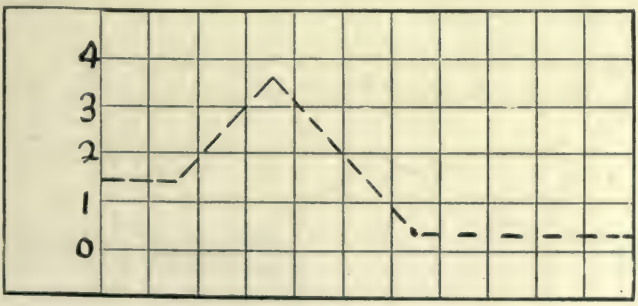

CHART 4.—Curve in eight of our poliomyelitic fluids: 1123210000.

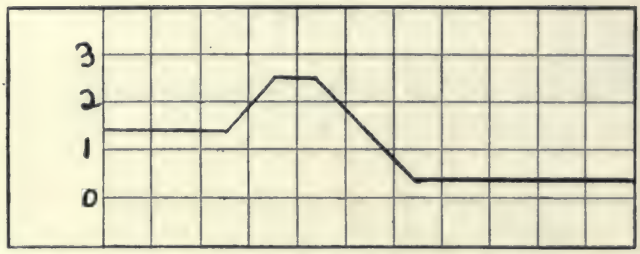

CHART 5.——Curve in six of our poliomyelitic fluids: 111221000.

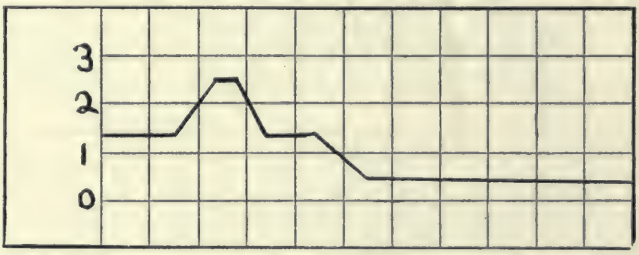

CHART 6.—Curve in five of our poliomyelitic fluids: 112110000.

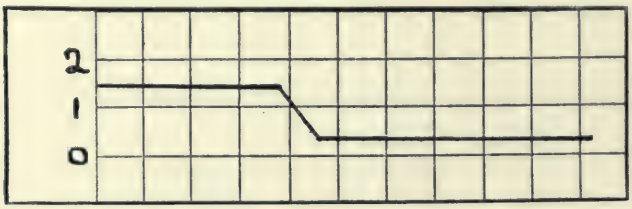

CHART 7.—Curve in fourteen of our poliomyelitic fluids: 111100000.

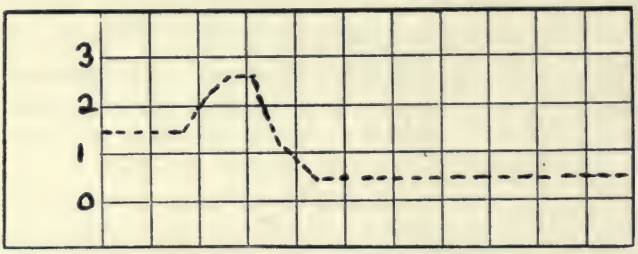

CHART 8.—Curve in four of our poliomyelitic fluids: 1121000000.

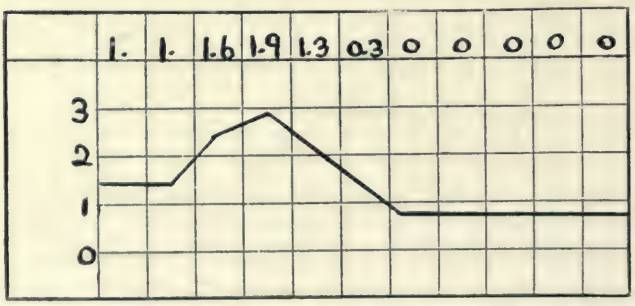

CHART 9.—Composite curve in 114 poliomyelitic fluids: 1122100000.

Every poliomyelitis fluid examined gave a curve falling in one of these six groups, or approximately so, but this cannot be taken to be of absolute diagnostic value, since a few fluids from patients with epidemic and tuberculous meningitis also fell in these groups. Of perhaps greater value is the differentiation of a poliomyelitic fluid, with a practically normal chemistry, and that of meningism. In only one instance was the fluid from a patient with poliomyelitis negative, even with a practically normal chemistry, while the curves from patients with meningism have been negative even with a slightly increased chemistry. Not enough fluids from patients with meningism have been as yet examined to enable us to feel sure that the fluids from them are always negative. If this proves to be true, the gold chlorid curve will be of great value in differentiating poliomyelitis fluid with slight chemical changes from fluids of meningism.

TABLE 10.—One Hundred and Fourteen Poliomyelitis Fluids Examined by Gold Chlorid Method

Seventy-seven of them fell in one of 6 curves as follows:

	No. of Cases
1122100000	40
1123210000	8
1112210000	6
1121100000	5
1111000000	14
1121000000	4

The other thirty-seven had various curves similar to the foregoing six, and are as follows:

	No. of Cases		No. of Cases		No. of Cases
1100000000	1	1221100000	2	22332100	1
1111100000	1	1222100000	2	22343210	1
1111110000	2	1223210000	3		2
1111111100	1	1222332100	1		
1111231100	1	1232100000	2		
1112100000	4	1233100000	1		
1112110000	2	1233210000	1		
1112221000	1		12		
1112233210	1				
1112321000	2				
1122110000	3				
1122210000	2				
1123321000	1				
1124432100	1				
	23				
	12				
	2				
	37				

Normal or meningism curve	0000000000 or 1110000000
Curve of 114 poliomyelitis fluids	1122100000
Curve of 13 tuberculous fluids	1112221000
Curve of 15 epidemic cerebrospinal meningitis	1111233210

2. QUANTITATIVE STUDIES IN SPINAL FLUIDS

JOSEPHINE B. NEAL, M.D., AND R. L. KAHN, SC.D.

Qualitative studies of the albumin, globulin and glucose, with rough quantitative estimations, have always been made by the meningitis division as a part of the routine examination of spinal fluids. The need of accurate quantitative determinations, however, has been keenly felt.

In view of the more extensive use now made of spinal fluid examinations for diagnosis, it would seem desirable to obtain as comprehensive a knowledge of the subject as possible. Moreover, there is always the hope and the possibility in studying such a new field, that some facts of practical value in the way of diagnosis and prognosis may be brought to light. It was, therefore, a source of great gratification to us when, in connection with the work of the epidemic of poliomyelitis in the summer of 1916, the opportunity was offered us to undertake such studies.

The determinations attempted embrace total, nonprotein, urea and ammonia nitrogen, uric acid, creatin, creatinin, sugar and cholesterol. The methods employed were the adaptations and, in some cases, modifications of the microchemical procedures used in blood investigations. These methods are described somewhat in detail at the end of the article.

With the exception of urea, which has been extensively studied by French workers, quantitative studies in spinal fluids are comparatively few, due, undoubtedly, to the fact that until recently, microchemical methods not being available, most single chemical tests required a larger amount of spinal fluid than was usually obtained at one puncture. Along all the lines of quantitative work the French have contributed most to the subject.

The work up to 1909 is reviewed by Anglada.[15] He gives various tables from different workers and concludes that the normal content of albumin in the spinal fluid is about 15 mg. per 100 c.c., and that normally, this albumin is serum-globulin, while in a true meningitis serum, albumin is also present and the total quantity is greatly increased, running as high as 300 mg. per 100 c.c. The normal urea is given as from 15 to 35 mg. per 100 c.c., and results as high as 438 mg. per 100 c.c. in uremia. The normal sugar is given as 0.045 to 0.055 per cent. He considers 0.06 to 0.10 per cent. or more, as an increase in the glucose, and cites such findings in diabetes and certain toxic and infectious conditions and diseases of the nervous system.

15. Anglada: Le liquide céphalorachidien, Paris, 1909.

In cases of meningitis and certain other conditions of the central nervous system, he finds a decrease in the sugar.

In a very complete and extensive study of spinal fluid, Mestrezat[16] gives in normal fluids, the following findings:

Albumin averages .....18 mg. per 100 c.c.; limit, 13 to 30 mg.
Urea averages ..... 6 mg. per 100 c.c.; limit, 3 to 10 mg.
Sugar averages.....0.053% per 100 c.c.; limit, 0.048 to 0.058%

In purulent meningitis the albumin is increased to 300 and even to 1,160 mg. per 100 c.c.; in tuberculous meningitis, from 100 to 300 mg. per 100 c.c.

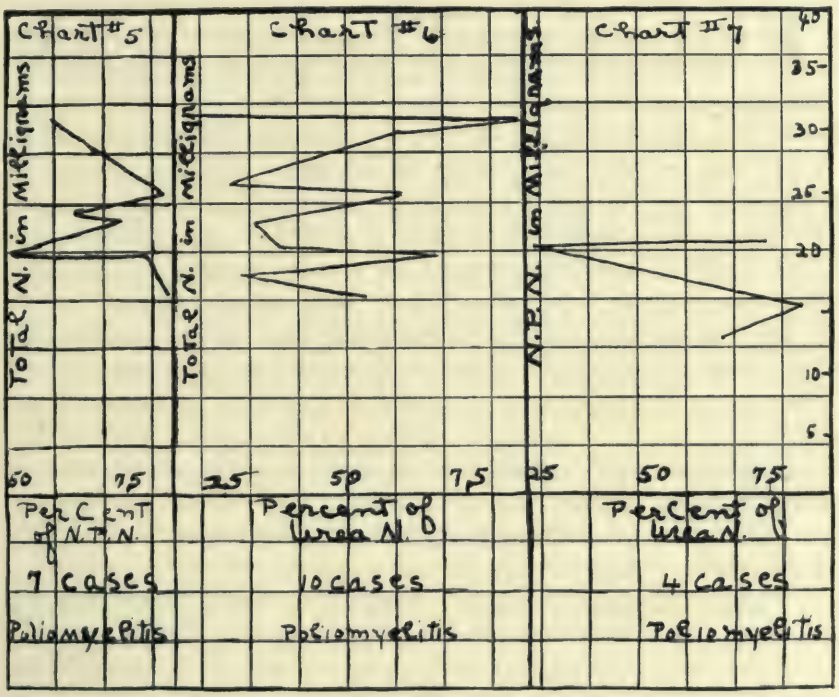

CHART 10

Soper and Granat[17] studied the urea in ninety-seven spinal fluids, having in mind, especially, the relation of the urea content to the prognosis in cases of uremia. The blood urea, also, was examined in certain cases and agreed closely with the content of the spinal fluid, as had been previously stated by other workers. They found the urea varying from 10 to about 50 mg. per 100 c.c. in conditions without nephritis, though in certain cases of tuberculous meningitis it rose to 170 mg. per 100 c.c. They give a very good review of the literature, the earlier work having been done mainly by French workers.

16. Mestrezat: Le liquide céphalorachidien normal et pathologique, Paris, 1912.
17. Soper and Granat: THE ARCHIVES INT. MED., 1914, **13,** 131.

According to Plaut, Rehm and Schottmuller,[18] normal spinal fluid contains from 30 to 60 mg. of protein per 100 c.c. These figures are increased in various diseases.

Pfeiffer, Kober and Field[19] studied a number of spinal fluids, mostly from syphilitic cases, with especial reference to the relation of the total protein, total globulin and euglobulin to the Wassermann reaction. They found the amount of protein varying from 20 to 100 mg. per 100 c.c. of fluid. Their fluids were nearly all pathologic.

Rosenbloom,[20] studying eleven fluids, found the nitrogen in spinal fluids varying from 0.172 parts per 100 in a normal fluid, to 0.362 in a case of meningitis.

Woods[21] found, in agreement with earlier workers, that the urea in the blood and spinal fluid was the same. He also observed that the total nonprotein nitrogen was about 25 per cent. lower than in the blood; that is, about 10 mg. per 100 c.c. of fluid. The urea was about 78 per cent. of the total nonprotein nitrogen; the total nonprotein nitrogen in cases of chronic nephritis varied from 17.85 to 188.69 mg. per 100 c.c., and the urea from 11.09 to 166.66 mg. per 100 c.c.

A similar relation between the nonprotein nitrogen in the spinal fluid and blood was reported earlier by Mollard and Froment.[22]

The concentration of urea in the spinal fluid, however, appears to be about equal to that in the blood, as is reported by Soper and Granat,[17] Cullen and Ellis[23] and other workers, referred to in the foregoing articles.

Fine and Myers[24] found that in nephritis the concentration of creatinin in the spinal fluid is 46 per cent., of creatin 22 per cent., of uric acid 5 per cent. of the concentrations of the respective substances in the blood.

Hopkins[25] studied the sugar content of the spinal fluid, comparing it in certain cases with the blood sugar, which he found to be, in normal conditions, about 10 mg. per 100 c.c. higher than in the spinal fluid. He determined the sugar content in 141 cases, including many conditions — meningitis, diabetes, infections, intoxications, epilepsy, nephritis, nervous diseases and syphilis. The earlier work along this line is reviewed.

---

18. Plaut, Rehm and Schottmuller: Leitfaden zur Untersuchung der zerebrospinal Flüssigkeit, Jena, 1913, p. 16.
19. Pfeiffer, Kober and Field: Proc. Soc. Exper. Biol. and Med., 1915, **12,** 153.
20. Rosenbloom: Biochem. Bull., 1916, **5,** 17.
21. Woods: The Archives Int. Med., 1915, **16,** 577.
22. Mollard and Fromet: Jour. de physiol. et de path. gén., 1909, **11,** 263.
23. Cullen and Ellis: Jour. Biol. Chem., 1915, **20,** 511.
24. Fine and Myers: Proc. Soc. Exper. Biol. and Med., 1916, **13,** 70.
25. Hopkins: Am. Jour. Med. Sc., 1915, **150,** 847.

Schloss and Schroeder[26] determined the sugar content of a large number of spinal fluids, both normal and pathologic, from infants and children. They concluded that the normal amount varies from 0.05 to 0.134 per cent. In tuberculous meningitis it varied from an amount too small to be determined to normal. In poliomyelitis it was normal in three cases and decreased in a fourth. In epidemic meningitis it was generally decreased at the height of the disease and increased with recovery, a fact previously noted by Connall[27] and by DuBois and Neal.[28] Kraus and Corneille[29] studied the sugar content in the spinal fluid in both normal and pathologic conditions. They found the range for normal fluids to be between 0.045 and 0.110 per cent. They also found a rise in the sugar content in recovering cases of epidemic cerebrospinal meningitis and a decrease in fatal cases.

The presence of cholesterol in spinal fluids has been reported by various workers[30] in different forms of paralysis.

In this laboratory the total nitrogen in poliomyelitis was found to be in the neighborhood of 25 mg. per 100 c.c. of spinal fluid. In various forms of meningitis, the total nitrogen was found to be considerably increased, extending from 35 mg. to about 150 mg. per 100 c.c. Total nitrogen determinations alone, however, are of comparatively little value in view of the variations of the nonprotein nitrogen content. This is perhaps well to emphasize, in view of the attempt of Landau and Halpern[31] to show that a certain antagonism exists between the total nitrogen and chlorids in spinal fluids; that a high finding of the one corresponds to a low finding of the other. A high total nitrogen may often be due to an increase in the nonprotein nitrogen, particularly in the presence of kidney disturbances.

The nonprotein nitrogen content in normal spinal fluid is about 50 to 70 per cent. of the total nitrogen, and urea about 60 to 80 per cent. of the nonprotein nitrogen. In pathologic conditions these relations do not hold.

The determinations of ammonia nitrogen were unsatisfactory, because sufficiently large quantities of a single fluid required for a test were not available. Mixed fluids, therefore, had to be resorted to. This procedure seemed justifiable in view of the fact that Frenkel-Heiden[32] was unable to demonstrate ammonia in spinal fluids. The findings show wide variation, with figures ranging from 0.1 mg. to

26. Schloss and Schroeder: Am. Jour. Dis. Child., 1916, **11,** 1.
27. Connall: Quart. Jour. Med., 1909-1910, No. 3, p. 152.
28. DuBois and Neal: Am. Jour. Dis. Child., 1915, **9,** 1.
29. Kraus and Corneille: Jour. Lab. and Clin. Med., 1916, **1,** No. 9.
30. Pighina: Ztschr. f. Phys. Chem., 1909, **61,** 508.
31. Landau and Halpern: Biochem. Ztschr., 1908, **9,** 72.
32. Frenkel-Heiden: Biochem. Ztschr., 1906, 1907, **2,** 188.

0.9 mg. of ammonia nitrogen per 100 c.c. of spinal fluid in poliomyelitis. It might be said, also, that these fluids, although sterile at the time of the determinations, had been kept in the ice-box for several weeks, which might slightly affect the results.

The determinations of uric acid also were carried out on mixed fluids. The results indicate that there are present from 0.25 mg. to 0.50 mg. of uric acid per 100 c.c. of fluid in poliomyelitis.

The quantity of creatinin in poliomyelitis fluid was found to be about 0.5 mg. per 100 c.c., and somewhat less than this amount of creatin. The recent conclusions of Gettler and Baker[33] that normal blood contains no more than 0.5 mg. per 100 c.c. of creatinin is of interest in this connection. If the method of Folin and Denis be correct, then, like urea, creatinin is equally distributed in the blood and spinal fluid.

The finding of sugar in poliomyelitis fluids are about normal, 0.06 per cent. In meningitis the findings are usually lower.

An attempt was made to determine cholesterol in spinal fluids by the method recently suggested by Bloor.[34] In no case, however, were the amounts sufficient for quantitative determinations. All fluids tested showed the presence of traces only.

The results in detail are given in the accompanying tables.[35]

METHODS

Total Nitrogen.—The method employed for the determination of total nitrogen in spinal fluids was a modification of the direct nesslerization method recently developed by Folin and Denis.[36] The modification in detail is presented in another place.[37] In this connection, only a brief outline of the procedure will be given.

Procedure: Two c.c. of spinal fluid are pipetted into a test tube, 1 c.c. of the concentrated acid mixture (containing 1 volume concentrated sulphuric acid, 3 volumes concentrated phosphoric acid and 1/15 volume of a 10 per cent. solution of copper sulphate) added and the digestion carried out over a microburner until the appearance of white sulphuric acid fumes. The mouth of the test tube is then covered with a watch glass and heating continued for about a minute. The color obtained is usually straw yellow. After permitting the test tube to cool, the contents are rinsed quantitatively into a 100 c.c. volumetric flask, using about 60 c.c. of water in the process. A quantity of 10 per cent. sodium hydroxid is then added sufficient to neutralize the concentrated acid and permit a surplus of 2 c.c. of alkali, and filtered. Into another 100 c.c. volumetric flask are pipetted 1 c.c. of the concentrated acid mixture, diluted, 20 c.c. of the standard ammonium sulphate solution containing 1 mg. ammonia nitrogen and an amount of 10 per cent. alkali solution equal to that added to the unknown. This is also made up to volume, shaken and filtered.

33. Gettler and Baker: Jour. Biol. Chem., 1916, **25,** 211.
34. Bloor: Jour. Biol. Chem., 1916, **24,** 227.
35. Dr. Kahn was assisted by Mr. Benjamin Shapiro in the technical work.
36. Folin and Denis: Jour. Biol. Chem., 1916, **26,** 473.
37. Kahn: Jour. Biol. Chem., 1916, **28,** 203.

Aliquot portions of these filtrates are employed for nesslerization. Thus, 50 c.c. of the water-clear filtrates of both the unknown and standard are pipetted into two 100 c.c. volumetric flasks, diluted to about 75 c.c. with water, and 10 c.c. of Nessler's solution added to each, made up to volume, shaken and the colors compared on the colorimeter. The same results could be obtained by using 50 c.c. volumetric flasks and employing 25 c.c. quantities of respective filtrates for nesslerization.

Nonprotein Nitrogen.—Procedure: To 5 c.c. of spinal fluid in a large test tube are added, quantitatively, 2 c.c. of a freshly prepared 25 per cent. solution of glacial phosphoric acid. The test tube is then stoppered, shaken and permitted to stand one to twenty-four hours and filtered through a small dry filter paper. Either 5 or 3 c.c. quantities of the water-clear filtrates are used for a nitrogen determination, the procedure being identical with that described for total nitrogen.

Urea Nitrogen.—Procedure: To 5 c.c. of spinal fluid in a 100 c.c. volumetric flask are added about 5 c.c. of water and 0.1 gm. of dry urease, shaken and permitted to stand at room temperature from twenty to forty minutes. This is then diluted with about 50 c.c. of water, 2 c.c. of freshly prepared glacial phosphoric acid added, also 0.5 gm. of Merck's charcoal, and made up to volume. This is shaken from time to time and allowed to stand for forty-five minutes or more, when it is ready to be filtered. Definite portions of the water-clear filtrates are used for nesslerization, as in the cases of the total and nonprotein nitrogen determinations.

Ammonia Nitrogen.—Procedure: To 25 c.c. spinal fluid are added 3 c.c. of glacial phosphoric acid, mixed, allowed to stand about an hour and filtered; 25 c.c. of the filtrate are pipetted into a 50 c.c. volumetric flask, 5 c.c. Nessler's solution added, made up to volume and compared with a standard ammonium sulphate solution containing 0.25 mg. nitrogen in 100 c.c.

Uric Acid.—Procedure: The Benedict[38] modification of the Folin and Denis[39] method was employed. Twenty-five c.c. spinal fluid are added to boiling hundredth normal acetic acid in a casserole, boiling continued for about a minute, removed from the flame, about 200 c.c. of boiling water added and poured over a folded filter. The filtrate is then concentrated to about 50 c.c., cooled, and about 0.5 c.c. of dialyzed iron added drop by drop, shaking with each addition, then filtered and the water-clear filtrate concentrated to about 2 to 3 c.c.; transferred quantitatively to a centrifuge tube, using about 5 c.c. of hot water to wash out the vessel. To the solution in the centrifuge tube is now added about 15 drops of ammonia-silver-magnesia mixture, allowed to stand for about ten minutes to permit precipitation, when it is centrifuged at a high speed for about five minutes. The supernatant fluid is poured off and excess of ammonia drawn off by inverting the tube on filter paper; 2 drops of a 5 per cent. solution of KCN are added to dissolve the precipitate. also 1 c.c. of the phosphotungstic acid reagent and about 8 c.c. of saturated solution of sodium carbonate. This is permitted to stand for a minute, transferred into a 25 c.c. or 50 c.c. volumetric flask, depending on the intensity of the color, made up to volume with water and compared with the standard on the Duboscq colorimeter. The latter is prepared by pipetting 5 c.c. of the uric acid standard solution into a 50 c.c. flask, and adding 2 drops of the KCN solution, 2 c.c. of phosphotungstic acid reagent and 15 c.c. of saturated sodium carbonate, and making up to the mark with water.

Creatinin and Creatin.—Procedure: For the determinations of creatinin and creatin the Folin and Denis[40] methods were employed. These methods have recently been criticized by McCrudden and Sargent.[41] The results, never-

38. Benedict: Jour. Biol. Chem., 1915, **20,** 629.
39. Folin and Denis: Jour. Biol. Chem., 1912-1913, **13,** 469.
40. Folin and Denis: Jour. Biol. Chem., 1914, **17,** 475.
41. McCrudden and Sargent: Jour. Biol. Chem., 1916, **26,** 527.

theless, seem worth repeating in view of the creatinin and creatin studies on blood by the same methods. To 5 c.c. of spinal fluid are added 20 c.c. of saturated solution of picric acid, filtered, and 10 c.c. quantities of the filtrate employed for creatinin and creatin determinations, respectively. The standards employed are solutions of creatinin in saturated picric acid. The color is developed by adding 0.5 c.c. of 10 per cent. sodium hydroxid solution and allowing to stand ten minutes. Several standards are prepared and the color of the unknown matched with the one which approached it closest in intensity. In the case of the creatin determinations, the standard also was autoclaved. This, it is believed, reduced the chances of error considerably.

Sugar.—This was determined by means of the Lewis and Benedict[42] method slightly modified.

Procedure: Four volumes of saturated solution of picric acid are added to 1 volume of spinal fluid, shaken and filtered. To 3 c.c. of the filtrate in a test tube graduated to the 10 c.c. mark is added 1 c.c. of saturated solution of sodium carbonate and placed in boiling water for about twenty minutes, after which it is cooled and made up to 10 c.c. with water. The standard employed is a solution of glucose (Kahlbaum) in saturated picric acid. To 3 c.c. of this solution containing 0.5 mg. of glucose is added 1 c.c. of saturated sodium carbonate solution, kept in a waterbath for about twenty minutes, cooled, made up to 10 c.c. and compared on the colorimeter with the unknown.

Seventy-five poliomyelitis fluids were tested for six substances — total nitrogen, nonprotein nitrogen, urea nitrogen, creatinin, creatin and sugar (Table 11). They showed the variations set forth in Table 12. The outcome of these seventy-five cases varied from complete recovery to death. The percentages of the substances named found in each fluid gave no indication of the final outcome.

Table 13 shows the results of the examination of spinal fluids in cases of purulent meningococcic, streptococcic and influenzal meningitis. Table 14 shows the results of successive punctures in the cases of epidemic cerebrospinal meningitis (E. C. S. M.) of Table 13. Twenty-three successive fluids from eight cases of epidemic cerebrospinal meningitis were tested for the six substances, total nitrogen, nonprotein nitrogen, urea nitrogen, creatinin, creatin and sugar. They showed the variations set forth in Table 15.

Table 16 shows the results of the examination of the spinal fluid in seventeen cases of tuberculous meningitis. Table 17 shows the variations in the findings of the substances examined for.

Table 18 gives the results of the examination of a number of fluids in various affections, and Table 19 shows the variation in total nitrogen, nonprotein nitrogen, urea nitrogen and sugar in six normal spinal fluids which were tested.

Table 20 gives the median of the total nitrogen, nonprotein nitrogen, urea nitrogen, creatin, creatinin and sugar in the various diseases. The median is used instead of the average, as it is the truer index of the greater incidence of values. It is obvious in estimating averages that a few very high or very low determinations will unduly influence the result.

42. Lewis and Benedict: Jour. Biol. Chem., 1915, **20**, 61.

TABLE 11.—Results of Spinal Fluid Examinations in Poliomyelitis

No.	Case	Quantitative Determinations						Qualitative Determinations*			Outcome
		Total N	Non-protein N	Urea N	Creatinin	Creatin	Sugar	Albumin	Globulin/	Fehling's	
2482a†	Polio.	.....	.....	.....	0.515	0.405	0.084	±,	±,	+++	Recovered
2516a	Polio.	.....	.....	.....	0.500	0.449	0.082	++,	+++,	+++	Both legs paralyzed
2535a	Polio.	.....	.....	.....	0.492	0.445	0.098	+,	+,	+++	O. K.
2517a	Polio.	.....	.....	.....	0.465	0.417	0.080	+,	+,	+++	8 weeks; slight weakness of arms and hands
2518a	Polio.	.....	.....	.....	0.454	0.495	0.092	+,	+,	+++	Recovered
2682a	Polio.	.....	.....	.....	.....	.....	0.088	+,	+,	+++	
2662a	Polio.	.....	.....	.....	.....	.....	0.059	+,	+,	++1	
2542a	Polio.	.....	.....	.....	.....	.....	0.053	++,	++,	+++	Recovered
2618a	Polio.	.....	.....	.....	.....	.....	0.072	++.	+1,	+++	Recovered
2685a	Polio.	.....	.....	.....	.....	.....	0.100	++1,	++1,	+++	Died
2792a	Polio.	.....	.....	.....	.....	.....	0.061	+,	+,	+++	No paralysis
2841a	Polio.	.....	.....	.....	.....	.....	0.087	+,	+sl.,	+++	Recovered
2884a	Polio.	.....	.....	.....	.....	.....	0.055	+1,	++,	+++	4 weeks; weak back; paralysis of lower extremities
2895a	Polio.	.....	.....	.....	.....	.....	0.025	+1,	+1,	+++	12 weeks; weakness of leg
2916a	Polio	.....	.....	.....	0.463	0.190	0.0602	+,	+,	+++	Recovered
3096a	Polio.	.....	.....	.....	0.273	.....	Traces	+sl.,	+,	++	O. K.
3101a	Polio.	.....	.....	.....	.....	.....	0.0742	+sl.	+,	++1	O. K.
3092a	Polio.	.....	.....	.....	0.560	.....	0.0742	+sl.,	+1,	+++	Died
3094a	Polio.	.....	.....	.....	0.360	.....	0.0523	+,	+,	++1	
3196a	Polio.	.....	.....	.....	0.388	0.319	0.0753	+sl.,	+sl.,	+++	Left deltoid; left facial paralysis
3197a	Polio.	.....	.....	.....	0.400	0.314	0.0781	++,	++,	+++	Died
3236b	Polio.	.....	.....	.....	0.387	0.448	0.0512	+,	+1,	+++	Weak left lower; brace
3241a	Polio.	25.00	20.95	15.68	0.400	0.314	0.0508	+,	+,	+++	8 weeks; double pelvic brace
3242b	Polio.	22.87	.....	6.93	0.350	0.350	0.060	+,	+,	+++	Weak right arm
3245b	Polio.	.....	.....	.....	0.326	.....	0.054	+++,	+++,	+++	Paralysis lower extremity
2994b	Polio.	.....	.....	.....	0.609	.....	0.0613	+,	++,	+++	Died
2989b	Polio.	.....	.....	.....	0.378	.....	Traces	+1,	+1,	++	Died
3007a	Polio.	.....	.....	.....	0.403	.....	.....	+,	+,	+++	Recovered
2998b	Polio.	.....	.....	.....	0.323	.....	0.0595	+,	+,	+++	Died
2979a	Polio.	.....	.....	.....	0.454	.....	0.0454	+sl.,	+,	+++	
3139a	Polio.	.....	.....	.....	.....	.....	0.1063	+,	+,	+++	Died
3140a	Polio.	.....	.....	.....	.....	.....	0.0552	+,	+,	+++	Died
3109a	Polio.	.....	.....	.....	.....	.....	0.0588	+,	+,	+++	
3274b	Polio.	.....	.....	.....	0.396	.....	0.0810	+,	+, (See 3274)	+++	No definite paralysis
3196b	Polio.	.....	.....	.....	0.429	.....	0.0824	+,	+, (See 3196 and 3360)	+++	Left deltoid; left facial paralysis
3274a	Polio.	.....	.....	.....	.....	.....	0.0641	+,	+,	+++	No definite paralysis
3207a	Polio.	.....	.....	15.25	.....	.....	.....	++,	++,	+++	Weak right deltoid
3252a	Polio.	17.33	.....	.....	.....	.....	.....	+,	+,	+++	O. K.

* The + marks in this column in all tables indicate the albumin, globulin and reduction of Fehling's solution, respectively.

† Successive fluids from the same cases are indicated by a, b, c, etc.

TABLE 11.—Results of Spinal Fluid Examinations in Poliomyelitis—(*Continued*)

No.	Case	Quantitative Determinations						Qualitative Determinations			Outcome
		Total N	Non-protein N	Urea N	Creatinin	Creatin	Sugar	Albumin	Globulin/	Fehling's	
3310b	Polio.	22.72	14.56	.....	.....	.....	.....	+,	+,	+++	8 weeks; left facial weakness
3314b	Polio.	33.30	.....	.....	.....	.....	.....	++,	++,	+++	Unable to sit up; left post. splint
3315c	Polio.	25.85	.....	6.62	.....	.....	.....	+,	+,	+++	8 wks.; weak lowers; slight weakness of uppers
3300a	Polio.	21.00	11.0(?)	.....	.....	.....	.....	+,	+, (See 3377)	+++	8 weeks; relaxed abdominal muscles
3307b	Polio.	24.25	.....	12.50	.....	.....	.....	++,	+1,	+++	Recovered
3322b	Polio.	.....	.....	12.50	.....	.....	.....	++1,	++1,	+++	8 weeks; left facial paralysis
3327c	Polio.	.....	13.72	.....	.....	.....	.....	++++,	++++,	++	O. K.
3324b	Polio.	.....	16.34	.....	.....	.....	.....	++++,	++++,	+++	Left deltoid weakness
3331a	Polio.	34.00	20.66	5.35	.....	.....	.....	++,	+,	+++	Died
3341b	Polio.	30.00	.....	18.51	.....	.....	.....	++,	++,	+++	O. K.
3342b	Polio.	.....	12.13	.....	.....	.....	.....	+,	+,	+++	No definite paralysis
3343b	Polio.	.....	12.08	.....	.....	.....	.....	+sl.,	+,	++++	No paralysis noted
3354a	Polio.	.....	.....	11.36	.....	.....	.....	++++,	++++,	+++	No definite paralysis; weak gluteals
3357b	Polio.	22.57	16.64	.....	.....	.....	.....	++,	+1,	+++	
3359c	Polio.	26.25	.....	.....	.....	.....	.....	+1,	+1,	++++	Weak right gluteals and right lumbar muscles
3196d	Polio.	19.50	15.54	13.12	.....	.....	.....	+1,	++,	+++	Left deltoid; left facial paralysis
3358d	Polio.	.....	14.01	.....	.....	.....	.....	++,	+1,	+++	8 wks.; posterior splints
3361c	Polio.	.....	17.87	.....	.....	.....	.....	++,	++1,	+++	Died
3310c	Polio.	.....	.....	9.61	.....	.....	.....	+1,	++,	+++	8 wks.; weak left quadriceps extensor
3376c	Polio.	18.42	.....	.....	.....	.....	.....	+,	+sl.,	+++	O. K.
3300b	Polio.	20.61	.....	7.81	.....	.....	.....	+1,	+1,	+++	Relaxed abdominal muscles
3322c	Polio.	.....	17.85	.....	.....	.....	.....	++,	++,	+++	Paralysis of left facial; 8 weeks
3379b	Polio.	16.87	.....	.....	.....	.....	.....	+,	+,	+++	8 wks.; slight facial paralysis; slight weakness of both quadriceps extensors
3384a	Polio.	20.00	.....	.....	.....	.....	.....	++,	++,	+++	Died
3324c	Polio.	20.68	.....	.....	.....	.....	.....	++,	++1, (See 3324)	+++	
3274c	Polio.	21.42	.....	.....	.....	.....	.....	++,	++, (See 3274)	+++	No definite paralysis
3397a	Polio.	16.37	13.72	8.83	.....	.....	.....	+,	+sl.,	+++	8 weeks; weak thigh and back muscles
3392a	Polio.	17.48	.....	5.06	.....	.....	.....	+1,	+1,	+++	Right arm and leg paralysis
3410c	Polio.	.....	.....	20.75	.....	.....	.....	+,	+1,	+++	Paralysis left quadriceps extensor
3341c	Polio.	.....	15.88	.....	.....	.....	.....	+1,	+1,	+++	O. K.
3412c	Polio.	22.62	.....	.....	.....	.....	.....	++,	+++,	+++	Right deltoid
3436a	Polio.	24.62	.....	14.62	.....	.....	.....	++,	++1,	+++	Died
3489a	Polio.	.....	24.78	.....	.....	.....	.....	++,	++1,	+++	Died
3497a	Polio.	31.25	.....	26.6	.....	.....	.....	+,	+,	+++	
2842a	Polio.	(?)	.....	.....	.....	.....	0.0523	+1,	++,	+++	
3523a	Polio.	16.87	8.91	.....	0.528	.....	0.0943	+1,	+1,	+++	

TABLE 12.—Findings in Successive Punctures

	Number of Fluids	Variation per 100 C.c., Mg.
Total nitrogen	24	16.37 to 34.00
Nonprotein nitrogen	16	8.91 to 24.78
Urea nitrogen	17	5.06 to 26.6
Creatinin	22	0.273 to 0.609
Creatin	11	0.190 to 0.495
Sugar	26	0.025 to 0.1063

TABLE 13.—Results of Examination of Spinal Fluids in Purulent Meningitis

No.	Case	Quantitative Determinations						Qualitative Determinations			Outcome
		Total N	Nonprotein N	Urea N	Creatinin	Creatin	Sugar	Albumin	Globulin	Fehling's	
3017a	Epidemic cerebrospinal meningitis	.....	.....	.....	0.595	.....	Traces	++++,	++++,	++	O. K.
3225a	Epidemic cerebrospinal meningitis	.....	.....	.....	0.326	.....	Traces	+++,	+++,	—	O. K.
3222c	Epidemic cerebrospinal meningitis	45.15	.....	14.12	.....	.....	.....	+++,	+++,	+++	O. K.
3268a	Epidemic cerebrospinal meningitis	34.25	15.86	.....	.....	.....	.....	++,	++,	+1	O. K.
3302b	Epidemic cerebrospinal meningitis	62.20	.....	10.25	.....	.....	.....	++++,	++++,	+	Died
3363a	Epidemic cerebrospinal meningitis	24.46	.....	.....	.....	.....	.....	++++,	++++,	++	O. K.
3386a	Epidemic cerebrospinal meningitis	39.80	.....	.....	.....	.....	.....	+++,	++++,	±	Died
3442a	Influenzal meningitis	40.25	.....	6.28	.....	.....	.....	++++,	++++,	—	Died
3468c	Influenzal meningitis	138.75	.....	.....	.....	.....	.....	++++,	++++,	—	Died
3472a	Influenzal meningitis	51.50	.....	.....	.....	.....	.....	++++,	++++,	±	Died
3500a	Streptococcus meningitis	86.30	.....	11.10	.....	.....	.....	++++,	++++,	—	Died
3541a	Epidemic cerebrospinal meningitis	69.50	46.66	15.15	67.1*	21.7†	Traces	++++,	++++,	—	
3574a	Epidemic cerebrospinal meningitis	.....	.....	.....	.....	.....	Traces	+++,	+++,	—	O. K.
3545b	Streptococcus meningitis	23.35	18.08	.....	77.4*	.....	0.075	++++,	++++,	—	

* Per cent. of nonprotein nitrogen in total.
† Per cent. of urea in total.

TABLE 14.—Results of Successive Punctures in Cases of Epidemic Cerebrospinal Meningitis

No.	Quantitative Determinations						Qualitative Determinations			Outcome
	Total N	Non-protein N	Urea N	Per Cent. of N. P. N. in Total	Per Cent. Urea in Total	Sugar	Albumin	Globulin	Fehling's	
3441										
2d puncture	120.0	33.47	21.62	.....	.....	.....	++++,	++++,	+	O. K.
5th puncture	36.75	.....	.....*	.....	.....	.....	+++,	+++,	++	
3473										
1st puncture	50.00	.....	.....	.....	.....	.....	++++,	++++,	—	O. K.
2d puncture	53.75	.....	.....	.....	.....	.....	++++,	++++,	+	
4th puncture	47.15	26.62	9.20	.....	.....	.....	++++,	++++,	+	
5th puncture	43.45	21.93	11.60	.....	.....	.....	++++,	++++,	+++	
3487										
1st puncture	95.00	45.83	36.48	.....	.....	.....	++++,	++++,	—	Died
2d puncture	250.00	136.25	53.28	.....	.....	.....	++++,	++++,	—	
3044										
4th puncture	73.50	26.60	.....	0.535*	0.704†	Traces	++++,	++++,	±	Died
5th puncture	.....	.....	.....	0.476*	.....	Traces	++++,	++++,	±	
6th puncture	.....	.....	.....	0.476*	.....	0.0628	++++,	++++,	±	
3512										
1st puncture	53.50	25.47		47.6		Traces	++++,	++++,	—	Died
4th puncture	29.37	13.62	.....	46.3	.....	Traces	++++,	++++,	—	
5th puncture	43.25	15.00	.....	34.6	.....	.....	++++,	++++,	—	
6th puncture	47.35	19.55	6.14	41.2	12.9	.....	++++,	++++,	—	
7th puncture	40.53	18.25	7.72	45.0	19.0	Traces	++++,	++++,	—	
8th puncture	48.50	19.55	7.54	40.3	15.5	Traces	++++,	++++,	—	
9th puncture	128.00	31.36	9.25	24.5	7.2	Traces	++++,	++++,	—	
3530										
1st puncture	52.00	21.85	10.41	42.0	20.0	Traces	++++,	++++,	—	O. K.
2d puncture	.....	.....	.....	.....	.....	.....	++++,	++++,	—	
3525										
1st puncture	36.10	20.58	10.25	57.0	28.3	Traces	++++,	++++,	—	O. K.
2d puncture	39.25	22.94	6.38	58.4	16.2	Traces	++++,	++++,	—	
3d puncture	46.25	21.77	9.25	47.0	20.0	Traces	++++,	++++,	—	
4th puncture	.....	.....	6.87	.....	.....	Traces	++++,	++++,	—	
5th puncture	71.00	25.69	9.61	36.1	13.5	Traces	++++,	++++,	—	
6th puncture	45.45	20.63	5.43	45.3	11.7	Traces	++++,	++++,	—	
7th puncture	86.00	27.36	9.85	31.8	11.4	Traces	++++,	++++,	—	
8th puncture	.....	.....	6.43	.....	.....	Traces	++++,	++++,	—	
13th puncture	.....	.....	9.47	.....	.....	.....	++++,	++++,	+++	
3551										
1st puncture	22.72	13.00	5.11	57.2	22.4	Traces	++++,	++++,	—	O. K.
3d puncture	.....	.....	3.66	.....	.....	Traces	+++,	++,	++	
4th puncture	.....	.....	6.77	.....	.....	.....	+++,	+++,	+	
5th puncture	.....	.....	4.55	.....	.....	.....	+++,	+++,	+++	

* Creatinin. † Creatin.

TABLE 15.—Results of Tests of Twenty-Three Successive Fluids from Eight Cases of Epidemic Cerebrospinal Meningitis Showing Variations

	Number of Fluids	Variations per 100 C.c. Mg.
Total nitrogen	9	22.72 to 250.00
Nonprotein nitrogen	9	13.00 to 136.25
Urea nitrogen	9	3.66 to 53.28
Creatinin	9	0.326 to 0.595
Creatin	9	0.704 to .....
Sugar	9	Traces to 0.0628
Per cent. nonprotein nitrogen in total	15	24.5 to 58.4
Per cent. urea nitrogen in total	15	7.2 to 28.3

If the termination was favorable, nitrogen, nonprotein nitrogen and urea were decreased; sugar was increased; if the termination was unfavorable, opposite results were obtained.

TABLE 16.—Results of Tests of Cerebrospinal Fluids in Tuberculous Meningitis

No.	Case	Quantitative Determinations						Qualitative Determinations			Outcome
		Total N	Nonprotein N	Urea N	Creatinin	Creatin	Sugar	Albumin	Globulin	Fehling's	
2508b	Tuberculous meningitis	.....	.....	.....	0.487	0.563	0.060	++,	+++,	+++	Died
2401a	Tuberculous meningitis	.....	.....	.....	0.765	0.735	0.028	+++,	+++,	+	
3115a	Tuberculous meningitis	.....	.....	.....	.....	.....	Traces	++,	++,	+sl.	Died
2966a	Tuberculous meningitis	.....	.....	.....	.....	.....	Traces	++,	++1,	++1	Died
3284a	Tuberculous meningitis	34.50	.....	6.66	.....	.....	.....	++,	+,	++	Died
3333a	Tuberculous meningitis	34.40	.....	.....	.....	.....	.....	++++,	++++,	+	
3339b	Tuberculous meningitis	29.70	17.25	7.93	.....	.....	.....	++++,	++++,	+++	Died
3335a	Tuberculous meningitis	42.50	.....	14.18	.....	.....	.....	++++,	++++,	—	
3434a	Tuberculous meningitis	24.35	.....	11.50	.....	.....	.....	++,	++,	+	Died
3304c	Tuberculous meningitis	26.50	13.88	7.06	.....	.....	.....	+++,	+++, (See 3284)	++	Died
3469a	Tuberculous meningitis	25.25	15.44	.....	.....	.....	.....	++++,	++++,	++	Died
3478b	Tuberculous meningitis	20.86	.....	.....	.....	.....	.....	++++,	++++,	++	Died
3514a	Tuberculous meningitis (?)	16.3	9.05	3.13	55.5*	19.2†	.....	++,	++,	—	
3520a	Tuberculous meningitis	23.35	12.82	.....	54.9*	.....	Traces	++++,	++++,	—	
3547a	Tuberculous meningitis	22.72	.....	.....	.....	.....	Traces	++++,	++++,	—	
3583a	Tuberculous meningitis	.....	.....	7.22	.....	.....	.....	++++,	++++,	+	
3584a	Tuberculous meningitis	.....	.....	4.54	.....	.....	.....	++++,	++++,	+	

* Per cent. of nonprotein nitrogen in total.
† Per cent. of urea in total.

TABLE 17.—Showing Variations in the Findings in Seventeen Cases of Tuberculous Meningitis

	Variations per 100 C.c., Mg.
Total nitrogen	20.86 to 34.50
Nonprotein nitrogen	12.82 to 17.25
Urea nitrogen	4.54 to 14.18
Creatinin	0.487 to 0.7652
Creatin	0.563 to 0.735
Sugar	Traces to 0.060

TABLE 18.—Results of Examination of Miscellaneous Fluids

No.	Case	Quantitative Determinations						Qualitative Determinations			Outcome
		Total N	Nonprotein N	Urea N	Creatinin	Creatin	Sugar	Albumin	Globulin	Fehling's	
2821a	Meningism; typhoid	.....	.....	.....	.....	.....	0.066	+,	+,	+++	
3095a	Meningism; endocarditis	.....	.....	.....	0.365	.....	0.0806	+,	+,	+++1	Died
3113b	Meningism; intestinal trouble	.....	.....	.....	.....	.....	0.0824	+sl.,	+sl.,	+++	O. K.
3244a	Possible brain tumor	.....	.....	.....	0.350	.....	0.051	+++,	+++,	+++	
3138a	Rheumatism	45.25	31.06	14.81	.....	.....	.....	+,	+,	+++	O. K.
?	Syphilis	23.35	19.38	.....	.....						
3251a	Cerebrospinal lues	.....	.....	.....	0.378	0.377	0.048	+,	+sl.,	+++	Improved
3240a	Normal (?)	14.35	.....	.....	.....	.....	.....	+,	+,	+++	
3495a	Normal	15.70	13.69	.....	.....	.....	.....	±,	+sl.,	+++	
3515a	Meningism	10.18	.....	6.46	.....	63.4†	.....	±,	±,	+++	
3516a	Meningism	15.30	13.68	.....	89.4*	.....	0.0888	±,	±,	+++	
3528a	Syphilis	19.45	14.15	.....	72.7*	.....	0.075	±,	±,	+++	
3529a	Meningism with pneumonia	9.67	.....	5.35	.....	55.3†	0.0923	±,	±,	+++	
3569a	Meningism	.....	.....	12.05	.....	.....	.....	±,	±,	+++	
3571a	Staph. albus meningitis	.....	.....	.....	.....	.....	Traces	++++,	++++,	±	
3593d	Meningism with pneumonia	22.72	22.38	10.00	98.5*	44.0†	0.0798	+,	+,	+++	

* Per cent. of nonprotein nitrogen in total.
† Per cent. of urea in total.

TABLE 19.—Showing Variations in the Findings in Six Normal Fluids

	Variations per 100 C.c., Mg.
Total nitrogen	9.67 to 15.70
Nonprotein nitrogen	13.68 to 13.69
Urea nitrogen	5.35 to 12.05
Sugar	0.0824 to 0.0923

TABLE 20.—MEDIAN CEREBROSPINAL FLUID FINDINGS IN VARIOUS DISEASES

	Total Nitrogen, Mg. per 100 C.c.	Nonprotein Nitrogen, Mg. per 100 C.c.	Urea Nitrogen, Mg. per 100 C.c.	Creatinin, Mg. per 100 C.c.	Creatin, Mg. per 100 C.c.	Sugar. Per Cent.
Poliomyelitis	22.57 25 cases	15.71 16 cases	12.50 17 cases	0.400 22 cases	0.405 11 cases	0.0613 37 cases
Epidemic cerebrospinal meningitis	47.25 30 cases	21.93 23 cases	9.25 26 cases	0.476 5 cases	0.704 1 case	Traces 23 cases
Tuberculous meningitis	25.88 10 cases	13.88 5 cases	7.14 8 cases	0.626 2 cases	0.649 2 cases	Traces 6 cases
Miscellaneous	23.04 14 cases	18.08 7 cases	10.00 7 cases	0.365 5 cases	0.377 1 case	0.075 12 cases

3. ANIMAL INOCULATION EXPERIMENTS

H. L. ABRAMSON, M.D.

POLIOMYELITIS IN MONKEYS FROM VIRUS OF THE 1916 EPIDEMIC

Landsteiner and Popper first produced poliomyelitis in monkeys in 1909. Since then workers in poliomyelitis the world over have performed similar experiments with success. This epoch-making discovery has served as an entering wedge to such workers as Landsteiner, Leviditi, Flexner and Lewis, Roemer and Joseph, Kling, Petterson and Wernstedt, and many others, who have greatly increased our knowledge of the etiologic agent of acute poliomyelitis.

The present work was instituted at the Bureau of Laboratories for the purpose of furnishing fresh material to the entire group of workers for the following studies:

1. Characteristics of the virus of the 1916 epidemic.
2. Isolation and cultivation of organisms said to be the cause of acute poliomyelitis.
3. Immunity problems, active and passive.
4. Problems of transmission.

The first attempts to produce the disease in monkeys resulted in failure. On account of lack of a fresh supply of monkeys, two animals, both of the rhesus variety, that had been the property of the department for several years, were used. These received heavy suspensions of material from the brain and cords of two patients that were clinically and pathologically undoubted cases of acute poliomyelitis. The animals received 0.5 c.c. of a 20 per cent. saline emulsion intracerebrally and 2 c.c. of the same suspension into the tissues around

each sciatic nerve. After one month's observation, these inoculations were repeated with the glycerinated material of the same cases, but in addition they received 10 c.c. of the virus suspension intraperitoneally. These inoculations were no more successful than the first. These monkeys, 98 and 102, later received massive inoculations by three routes, intracerebral, perisciatic and intraperitoneal, of known virulent material from a monkey of the second generation. This, too, proved unsuccessful. It was decided that these monkeys were very refractory and would serve as a source of immune serum for later experiments.

Brain and cord material from three new cases that were clinically positive cases of acute poliomyelitis was then inoculated by three routes, intracerebral, perisciatic and intraperitoneal, into two monkeys from a fresh supply, one being a rhesus and the other a sapajou, a South American ring tail monkey. They received 0.5 c.c., 2 c.c. and 10 c.c. of a 20 per cent. suspension of this material, respectively, in the three ways above mentioned.

On the seventh day after the inoculation, Monkey 1, *Macaccus rhesus,* presented tremor of the head and weakness in the left leg. This condition progressed to complete paralysis of all the limbs, first the left leg, then right leg, left arm, right arm, convulsions and respiratory failure. The monkey died on the third day after the appearance of the muscular weakness. Monkey 2, sapajou, exhibited no symptoms at this writing, three and one-half months after inoculation. Two other animals of this variety were subsequently inoculated with a virulent virus, but these, too, were unsuccessful, confirming the unsuitability of this type of monkey for experimental work in the study of poliomyelitis.

No further difficulty was experienced in passing the virus obtained from Monkey 1 through a series of sixteen monkeys, fourteen of the rhesus variety and two South African mangabeys. The virus is now in the eighth generation and exhibits evidence of increased virulence.

The animals of the second and third generations were inoculated with heavy suspensions of the brain and cord material by the three ways, intracerebral, perisciatic and intraperitoneal, but subsequent animals were infected by injection of 0.5 c.c. of 10 per cent. suspensions into the brain. The last two animals received 0.5 c.c. of 5 per cent. suspension intracerebrally.

TECHNIC

The technic followed was that in use at the laboratory for the preparation of antirabic treatments. Fresh brain and cord material was weighed and ground up in a sterile mortar and sterile salt solution added to make the desired strength. The intracerebral inoculations were made always into the right cerebral hemisphere. The animals were anesthetized. An incision was made in the middle of the scalp over the forward part of the skull. The wound was retracted to the right side and a small trephine opening made with an awl

in the right frontal bone ¼ inch anterior to the coronal suture, just to the right of the sagittal suture. The suspension was injected very slowly. It is well not to incise the pericranium, for, if intact, it acts as a valve over the site of the trephine opening and prevents the escape of the injected material. The retracted scalp when it resumes its normal position also aids in the prevention of leakage. In performing the perisciatic inoculations, care was taken to place the needle in close relation to the posterior aspect of the middle of the femur before expelling the material.

Of the seventeen animals inoculated, all but two, *Macacus rhesus* 50 and 51, exhibited frank signs of paralysis. On the fourth day after the inoculation, No. 50 became quite subdued and huddled in a corner of the cage. On being forced to move, it was noticed that he limped slightly on the left hind leg. This animal then received two intraspinal injections of serum obtained from *Macacus rhesus* 102 on successive days. The animal seemed to improve rapidly, and at this date shows no weakness in any limb.

Macacus rhesus 51 exhibited symptoms of distress on the fourth day after inoculation, which consisted of tremors and general weakness; but showed no evidence of paralysis in any limb. This general muscular weakness progressed and the monkey died on the third day after onset of symptoms. The brain showed hyperemia, and sections of the cord presented redness and swelling of the gray matter. The lungs and other organs were apparently normal. This form of the disease in monkeys has been encountered many times by workers in this field and has been called the marantic type of monkey poliomyelitis. Subsequent inoculations with material from this animal produced the typical spinal type of paralysis.

The incubation period in this series was from four to thirteen days. Eight, or 47 per cent., developed paralysis on the seventh day; two on the eighth day; two on the fourth day, and one each on the fifth, tenth, eleventh, twelfth and thirteenth days after the inoculation.

Twelve of the seventeen animals died, a mortality of 71 per cent. Of the remaining five, four exhibit residual paralyses. The average duration of illness for eleven of the twelve fatal cases was four days, the limits being two and seven days. *Macacus rhesus* 25 died twenty days after onset of paralysis. This animal had been inoculated with brain and cord material from a rabbit that had exhibited flaccid paralysis of a progressive type. This inoculation produced no effects, and after an observation period of six weeks, was again inoculated along with two other animals, 36 and 37, with material from No. 26, fourth generation. The incubation period of Nos. 36 and 37 was seven days. That of No. 25 was thirteen days. With the onset of symptoms the paralysis progressed rapidly for three days. Then the process appeared to subside and the animal improved over a period of nearly two weeks. After this quiescent period, the paralysis began where it had left off,

and the animal died of respiratory failure on the twentieth day of the disease.

The character of the paralysis in all but two of the animals was that of the progressive, spinal type, beginning in the left leg, progressing to the right leg, left arm, right arm, and, in the fatal cases, to respiratory paralysis. In one animal, paralysis appeared first in the right leg, then left leg, left arm, right arm, and paralysis of respiration. In the other, the symptom appeared first in the left arm, right arm, then simultaneously in both legs and respiratory paralysis. In the nonfatal cases, except No. 50, the paralysis extended to the left arm, leaving the right arm untouched. With the cessation of the progress of the disease, the left arm recovered its power to some extent, but the paralysis of the legs was permanent.

The gross pathologic changes presented a similar appearance in all the fatal cases, consisting in moderate congestion of the pial vessels of brain and cord. Cut sections of cord at various levels presented a reddening and swelling of the gray matter, rendering it distinct and prominent.

The microscopic picture presented congestion and edema; some capillary hemorrhage; perivascular and also diffuse round cell infiltration; ganglion cells in various stages of destruction and neuronophagia; all the changes present in human cases, except that they are more severe.

Passage of this virus will be continued with the hope of increasing its virulence so as to permit to use filtrates in further work.

Appended is a chronologic table of protocols of the animal work here recorded.

SERUM THERAPY IN EXPERIMENTAL POLIOMYELITIS

The blood of persons who have survived an attack of acute poliomyelitis contains specific substances which possess the ability to neutralize active poliomyelitis virus. This has been demonstrated by Flexner and Lewis, Roemer, Landsteiner and Leviditi, and others. It has also been shown that monkeys recovering from an attack of poliomyelitis become refractory to a second inoculation of virulent material, and in the blood of these animals can be demonstrated the neutralizing principles found in the blood of recovered human cases.

Netter[43] applied this knowledge in the treatment of a small series of human cases, with perhaps favorable results. His conclusions were not very definite. He administered, intraspinally, from 4 to 12 c.c. of serum obtained from a recovered case whose blood yielded a negative Wassermann. It was administered daily for four or five days, or as

43. Netter: Bull. de l'Acad. de méd., 1914, **66**, 525.

long as the clinical symptoms indicated its need. One case received eight injections.

Zingher,[44] of the Bureau of Laboratories, treated a larger number of patients by the intraspinal method, using serums obtained both from recovered cases of the disease and from normal persons. His report reads favorably to the treatment.

No tests were made to determine whether or not the serums obtained from the recovered patients possessed the neutralizing powers necessary to render it specific. Two cases of reinfection in the epidemic of the past summer, that had come to our attention, may throw some doubt on the assumption that all persons who recovered from one attack of the disease are immune to a second infection, or that the blood of all such persons possesses neutralizing powers.

The testing of the serum of each donor, however, for the specific principles would render the whole procedure impracticable, mainly because of the loss of time necessary to perform this test, and secondarily, because of the expense, for at the present time there is no way of demonstrating this property in serum, except by the injection into a monkey of active virus that had been placed in contact with the serum. From a practical point of view, the probabilities are that only a small percentage of the cases would give a negative test.

Schwartz[45] treated twenty-one patients with convalescent human serum. Of these, nine recovered without paralysis. Of a series of twenty-one other patients treated expectantly, seventeen recovered without paralysis. From this it might be inferred that the serum was of no particular advantage. Schwartz feels that too much was not to be expected of the use of the immune serum.

Prognosis in poliomyelitis is a difficult matter. Poliomyelitis is a very erratic disease and predictions as to the course it will follow in a given case are many times guess work. It will require, therefore, great numbers of cases adequately controlled to gain a true idea of the value of the serum treatment from the clinical point of view.

The clinical use of the serum of patients in old recovered cases of poliomyelitis is not founded on complete, clearcut animal experimentation. Its use is in part scientific, and in part empirical.

Flexner and Lewis[46] performed two experiments, the results of which indicate that a known specific serum may exert a prophylactic effect. An effective dose of active virus was injected intracerebrally into a monkey. Within twenty-four hours after the inoculation, and daily thereafter, the animal received intraspinal injections of immune

44. Zingher: Arch. Pediat., 1916, **33,** 872.
45. Schwarz: Arch. Pediat., 1916, **33,** 859.
46. Flexner and Lewis: Jour. Am. Med. Assn., 1910, **54,** 1780, and **55,** 662.

serum for a number of days. This animal remained healthy, whereas the control died. Another monkey was inoculated by intranasal scarification with a potent virus. This animal received intraspinal injections of immune serum within twenty-four hours after the inoculation, and at three-day intervals for a number of injections. This monkey did not exhibit any symptoms of poliomyelitis, while the control died of the disease. The authors state that if the quantity of virus injected is not in excess of a certain amount, the procedure described will serve to protect animals injected with such a quantity of virus.

The conditions of these experiments, however, do not parallel those which are met with when dealing with actual human cases, in which the virus has already become established and is multiplying in the central nervous system, as evidenced by the symptoms of the disease. In this instance the specific serum no longer can prevent; it must cure. It must counteract and nullify virus that has already become parasitic and that may have increased in amount, perhaps in excess of that which can be taken care of by injections of known immune serum.

The present work in experimental serum therapy was undertaken in an attempt to supply the conditions that are met with in actual practice. This work comprises six experiments in each of which were used two animals. One animal was serum-treated and the other acted as a control. The virus was emulsion of brain and cord material derived from the epidemic of the past summer. Virus of the second generation was used in the first series, and the virus of each succeeding generation was used in the remaining experiments. The amount of virus injected was not determined from very much previous experience with this strain. That the dosage was not excessive is evidenced by the fact that two of the control animals, 37 and 54, and two others, 23 and 24, not used in these experiments, but which received the same amounts of virus, survived the disease.

The serum used in these experiments was obtained by heart-puncture from Monkeys 98 and 102. Both of these animals were resistant to the effects of three inoculations of brain and cord material. This material was inoculated in heavy suspensions intracerebrally, in the tissues about the sciatic nerves and in the peritoneum. The material for the first two inoculations was derived from two human cases, clinically and pathologically positive cases of poliomyelitis. The third inoculation was with material of the second generation monkey virus. These inoculations were given three weeks apart. It was assumed that as a result of these three inoculations, these monkeys were immune and that the blood of these animals ought to contain the specific antibodies. No neutralization test was performed on the serums used in this set of experiments. This, in a measure, parallels the clinical use of serum by Netter and Zingher.

In a series of experiments now under way we shall have the opportunity of observing the effects of known monkey and human immune serum in the experimental serum therapy of monkey poliomyelitis.

Method of Injection.—The serum was injected intraspinally by syringe in doses of 2 to 3.5 c.c., depending on the size of the animal and resistance offered to the plunger of the syringe. As much spinal fluid as possible was withdrawn, usually with the aid of the syringe. The first tap yielded up to 2 c.c. of slightly turbid fluid, but subsequent punctures yielded from 0.5 to 1 c.c. of fluid. The fluids, on being examined, when the quantity was sufficient, gave a globulin test and a definite increase in cells; in one instance, 690 cells per cubic millimeter. The serum was injected very slowly and with extreme caution against using any excess pressure. Only one animal exhibited severe effects after the intraspinal injection. These consisted of marked rigidity of limbs, retracted neck and labored and rapid respiration. They were, however, very transient and within a half hour after the injection the monkey appeared as before the injection. Retraction of the neck was noted after many of the injections, particularly after the symptoms of paralysis had appeared.

Time of Injection.—The time periods elapsing between the injection of the virus and the beginning of the intraspinal serum injections was so arranged as to be applicable to conditions met with in actual practice. In Experiments 1 and 2 the serum treatment was begun on the first day of the appearance of any muscular weakness. In the remaining four experiments serum treatment was instituted before any symptoms had appeared, corresponding to the preparalytic stage in the human disease.

The protocols are as follows:

EXPERIMENT 1.—Sept. 1, 1916. M. rhesus 50, injected with 0.5 c.c., intracerebrally, 2 c.c. perisciatic, and 10 c.c. intraperitoneally, of 10 per cent. suspension Generation II virus. M. rhesus 51, control, received 0.5 c.c., intracerebrally, of the same emulsion.

Sept. 6, 1916, No. 50 appeared sick and limped on left leg. Received 3.5 c.c. Serum 102, intraspinally. Sept. 7, 1916, 3.5 c.c. Serum 102, intraspinally. Limp still present. September 10 the limp was not noticeable and the animal appeared strong and healthy.

Sept. 5, 1916, M. rhesus 51, control, exhibited general tremors and marked muscular weakness; no definite paralysis. Died Sept. 8, 1916. Congestion of pia and swelling and reddening of gray matter of cord. The virus of this monkey subsequently produced typical flaccid paralysis.

Whether or not M. rhesus 50 really had poliomyelitis, it is difficult to judge. He did not at any time present frank paralysis and his rather rapid recovery is suspicious. This animal was one of whose past history we knew nothing.

EXPERIMENT 2: Sept. 21, 1916, Rhesus 27, 0.5 c.c. intracerebrally and 2 c.c. perisciatic, of 10 per cent. virus, Generation III; Rhesus 26, control, 0.5 c.c. intracerebrally, same virus.

Sept. 28, 1916, Rhesus 27; weakness left leg; 2.5 c.c. Serum 102 intraspinally. Rhesus 26, control; paralysis left, and weakness right leg.

Sept. 29, 1916, Rhesus 27, paralysis both legs; weakness left arm; 2.5 c.c. Serum 102, intraspinally. Rhesus 26, paralysis both legs; left arm; weakness right arm; difficulty in breathing.

Sept. 30, 1916, Rhesus 27, complete paralysis of limbs and diaphragmatic breathing. Died. Rhesus 26, respiratory failure. Died.

The incubation period in both of the animals was eight days and duration of illness three days.

EXPERIMENT 3: Oct. 2, 1916, Rhesus 36, 0.5 c.c. 10 per cent. virus, Generation IV, intracerebrally. Rhesus 37, control, 0.5 c.c. same suspension, intracerebrally.

Oct. 7, 1916, Rhesus 36, apparently normal; 3 c.c. Serum 102, intraspinally. Rhesus 37, well.

Oct. 8, 1916, Rhesus 36, well; 3 c.c. Serum 102. Rhesus 37, O. K.

Oct. 9, 1916, Rhesus 36, paralysis both legs; weakness left arm; 2.5 c.c. Serum 102. Rhesus 37, control; paralysis left leg; weakness right leg.

Oct. 10, 1916, Rhesus 36, complete paralysis both arms and legs; breathing with difficulty; no serum; condition bad. Rhesus 37, paralysis both legs; weakness left arm; does not appear as sick as 36.

Oct. 12, 1916, Rhesus 36, died of respiratory paralysis. Rhesus 37, paralysis of both legs; weakness left arm; cessation of progress of paralysis.

Nov. 29, 1916, Rhesus 37, alive; permanent paralysis in legs; left arm O. K.

In this experiment Rhesus 36 received serum treatment on the fifth day after injection of virus and two days before the onset of paralysis. Rhesus 37, control, exhibited paralysis on the same day as No. 36, an incubation of seven days. The serum treatment apparently had no influence on the incubation period. Furthermore, No. 36, despite three treatments, suffered a rapidly spreading, fatal form of the disease, whereas No. 37, control, survived the same injection, but with residual paralyses.

Experiment 4: Oct. 13, 1916, Rhesus 43, 0.5 c.c., 10 per cent., Generation V virus, intracerebrally. Rhesus 42, control, a very large animal, 1 c.c. intracerebrally and 5 c.c. intraperitoneally of same virus.

Oct. 18, 1916, Rhesus 43 received intraspinally, 3 c.c. Serum 102; October 19, 2.5 c.c. same serum; October 20, 3 c.c. Serum 102; October 21, 2.5 c.c. Serum 98; October 22, 2 c.c. Serum 98. No signs of disease during this period. Rhesus 42, control, presented no symptoms.

Oct. 23, 1916, Rhesus 43, left leg paralyzed and weakness in right leg; 2 c.c. Serum 98 given intraspinally. Rhesus 42 shows no symptoms.

Oct. 24, 1916, Rhesus 43, paralysis progressing; 2.5 c.c. Serum 102 administered. Rhesus 42 apparently well.

Oct. 25, 1916, Rhesus 43, paralysis involving both arms and legs; 3 c.c. Serum 102 given. Rhesus 42, control, shows weakness in left leg.

Oct. 27, 1916, Rhesus 43, died of respiratory paralysis. Rhesus 42 presents involvement of both legs and weakness of left arm.

Oct. 31, 1916, Rhesus 42 died of respiratory paralysis.

In the foregoing experiment, the serum treated animal began to receive intraspinal injections of serum on the fifth day after the injection of the virus and five days prior to the appearance of symptoms in the same animal, and seven days before the control animal exhibited muscular weakness. Furthermore, the control animal had several times the dose of virus received by the test animal. The progress of the disease was more rapid in the serum treated animal, which terminated on the fifth day of the disease, than in the control animal, which died on the seventh day of the disease.

Experiment 5: Nov. 2, 1916, Rhesus 52, 0.5 c.c. 10 per cent. Generation VI virus intracerebrally.

Oct. 31, 1916, Rhesus S, large animal, control, 0.5 c.c. intracerebrally and 5 c.c. intraperitoneally, of 10 per cent. Generation VI virus used on No. 52.

Nov. 8, 1916, Rhesus 52, apparently normal, received 2.5 c.c. Serum 102 intraspinally. Rhesus S, control, showed paralysis of left arm.

Nov. 9, 1916, Rhesus 52, paralysis of left leg; 2.5 c.c. Serum 102. Rhesus S, paralysis of all limbs and respiratory paralysis. Died.

Nov. 10, 1916, Rhesus 52, paralysis progressing; 2.5 c.c. Serum 102.

Nov. 11, 1916, Rhesus 52, paralysis of both legs and left arm; 2 c.c. serum 98 administered.

Nov. 13, 1916, Rhesus 52, complete paralysis, including muscles of respiration. Died.

Though Rhesus 52 received a smaller dose of virus and one injection of serum on the sixth day after the inoculation, the incubation period was seven days,

TABLE 21.—Chronologic Table of Protocols

No.	Species	Generation	Date of Injection	Incubation, Days	Amount of Injection, C.c.	Strength, per Cent.	Site of Injection	Duration of Disease, Days	Character of Paralysis	Outcome
1	M. rhesus	I	8/12/16	7	0.5 2 5	20 20 20	Brain Perisciatic Peritoneum	3	Progressing spinal, beginning in left leg	Died 8/22/16
10	M. rhesus	II	8/23/16	7	0.5 2 10	20 20 20	Brain Sciatic Peritoneum	3	Progressing spinal, beginning in left leg	Died 9/1/16
50	M. rhesus	III	9/ 1/16	4	0.5 2 10	10 10 10	Brain Sciatic Peritoneum	3	Slight weakness in left leg.....	Recovered with out paralysis
51	M. rhesus	III	9/ 1/16	4	0.5	10	Brain	3	General muscular weakness; marantic type	Died 9/7/16
24	M. rhesus	IV	9/ 9/16	5	0.5	10	Brain	4	Progressing spinal, beginning in left leg; cessation of process; both legs and left arm involved	Recovered with residuals
26	M. rhesus	IV	9/21/16	7	0.5 (No. 51)	10	Brain	3	Rapidly progressing spinal, beginning with left leg	Died 10/10/16
27	M. rhesus	IV	9/21/16	7	0.5 (No. 51)	10	Brain	3	Rapidly progressing spinal, beginning with left leg	Died 10/1/16
36	M. rhesus	V	10/ 2/16	7	0.5	10	Brain	4	Rapidly progressing spinal, beginning with left leg	Died 10/12/16
37	M. rhesus	V	10/ 2/16	7	0.5	10	Brain	5	Progressing spinal, beginning with left leg; progressed as far as left arm	Recovered with residuals
25	M. rhesus	V	10/ 2/16	13	0.5	10	Brain	20	Slowly progressive spinal, beginning in left leg	Died 11/3/16
42	Giant M. rhesus	VI	10/13/16	12	0.5 5	10 10	Brain Peritoneum	7	Progressing spinal, left leg.....	Died 10/31/16
43	M. rhesus	VI	10/13/16	10	0.5	10	Brain	5	Progressing spinal, left leg.....	Died 10/27/16
S	M. rhesus	VII	10/31/16	8	0.5 5	10 10	Brain Peritoneum	2	Progressing spinal, left leg.....	Died 11/9/16
52	M. rhesus	VII	11/ 2/16	7	0.5	10	Brain	5	Progressing spinal, left leg.....	Died 11/13/16
53	Mangabey	VIII	11/10/16	7	0.5	5	Brain	6	Progressing spinal, beginning in right leg	Died 11/22/16
54	Mangabey	VIII	11/10/16	8	0.5	5	Brain	7	Progressing spinal, left leg, and weakness of right leg and left arm	Appears to be recovering
23	M. rhesus	VIII	11/15/16	11	0.5	10	Brain	4	Weakness of left and right legs.....	Appears to be recovering

TABLE 22.—Summary of Experiments on

No.	Species	Generation	Virus Injected				Serum Injection Intraspinously		
			Amount, C.c.	Strength, per Cent.	Site	Date	Date	Amount, C.c.	Source, Serum
50	Rhesus	II	0.5 2 10	10 10 10	Brain..... Sciatic..... Peritoneum	9/ 1/16	9/ 6 9/ 7	3.5 3.5	102 102
51	Rhesus Control	II	0.5	10	Brain	9/ 1/16	.....	.....	.....
27	Rhesus	III	0.5 2	10 10	Brain..... Sciatic.....	9/21/16	9/28 9/29	2.5 2.5	102 102
26	Rhesus Control	III	0.5	10	Brain	9/21/16	.....	.....	.....
36	M. rhesus	IV	0.5	10	Brain	10/ 2/16	10/ 7 10/ 8 10/ 9	3 3 2.5	102 102 102
37	Rhesus Control	IV	0.5	10	Brain	10/ 2/16	.....	.....	.....
52	Rhesus	VI	0.5	10	Brain	11/ 2/16	11/ 8 11/ 9 11/10 11/11	2.5 2.5 2.5 2	102 102 102 98
S	Rhesus (large) Control	VI	0.5 5	10 10	Brain, intraperitoneally	11/31/16	.....	.....	.....
53	Mangabey	VII	0.5	5	Brain	11/10/16	11/15 11/16 11/18 11/19	3 3 2.5 2	102 102 98 98
54	Mangabey Control	VII	0.5	5	Brain	11/10/16	.....	.....	.....
43	Rhesus	V	0.5	10	Brain	10/13/16	10/18 10/19 10/20 10/21 10/22 10/23 10/24 10/25	3 2.5 3 2.5 2 2 2.5 3	102 102 102 98 98 98 102 102
42	Giant rhesus Control	V	1 5	10 10	Brain..... Peritoneum	10/13/16	.....	.....	.....

INTRASPINAL TREATMENT WITH UNKNOWN "IMMUNE" SERUM

Date	Incubation, Days	Duration of Disease, Days	Paralysis: Character, Extent	Outcome
9/6	5	2	Slight weakness in left leg.....	Alive and well
9/5	4	8	General muscular weakness; marantic type.....	Died 9/8/16
9/28	8	3	Rapid progressive paralysis, left leg, right leg, left arm and right arm; resp. failure	Died 9/30/16
9/28	8	3	Rapid progressive paralysis, left leg, right leg, left arm, right arm; resp. failure	Died 9/30/16
10/9	7	4	Rapid progressive paralysis beginning with left leg; right leg, left arm, right arm; resp. paralysis	Died 10/12/16
10/9	7	4 acute	Progressive flaccid paralysis beginning with left leg; right leg, left arm, then regression	Alive; has diplegia
11/9/16	7	5	Progressive spinal, beginning with left leg; then right leg, left arm, right arm	Died 11/13/16
11/8/16	9	2	Rapid progressive spinal, beginning with left arm; then right, then resp. failure	Died 11/9/16
11/7/16	7	6	Progressive spinal paralysis, beginning with right leg; then left leg, left arm, right arm; resp. failure	Died 11/22/16
11/18/16	8	8	Progressive spinal paralysis, beginning with left leg; weakness right leg and left arm; slight weakness in right arm	Alive and improving
10/23/16	10	5	Progressive flaccid paralysis beginning with left leg, then right leg, then left arm, then right arm; resp. failure	Died 10/27/16
10/25/16	12	7	Progressive spinal paralysis, beginning with left leg, then right leg; simultaneously in both arms; resp. failure	Died 10/31/16

whereas in Rhesus S, with larger dosage, and no serum therapy, the incubation was nine days. This animal, however, suffered a fulminating type of disease, dying on the second day after the appearance of symptoms. This was probably due to the early involvement of muscles of respiration. The serum treated animal died on the fifth day of the disease.

EXPERIMENT 6: Nov. 10, 1916, Mangabey 53, 0.5 c.c. 5 per cent. Generation VII virus, intracerebrally. Mangabey 54, control, 0.5 c.c. 5 per cent same virus, intracerebrally.

Nov. 15, 1916, Mangabey 53, appears well; 3 c.c. Serum 102, intraspinally.

Nov. 16, 1916, Mangabey 53, 3 c.c. Serum 102, appears normal.

Nov. 17, 1916, Mangabey 53, paralysis of left leg; no serum.

Nov. 18, 1916, Mangabey 53, paralysis progressing; 2.5 c.c. Serum 98. Mangabey 54, weakness left leg.

Nov. 19, 1916, Mangabey 53, paralysis both legs and left arm; 2 c.c. Serum 98 administered. Mangabey 54, marked weakness in left leg and slight weakness in right leg; progress of paralysis slow.

Nov. 20, 1916, Mangabey 53, lies prone; does not stir body; moves right arm weakly; tremor of head. Mangabey 54, condition about the same as before.

Nov. 22, 1916, Mangabey 53, complete paralysis. Died. Mangabey 54, weakness in legs more marked.

Nov. 25, 1916, Mangabey 54, progress of involvement slow; shows slight weakness of left arm; tremor of head.

Nov. 27, 1916, Mangabey 54, shows signs of improvement; left arm apparently stronger, as is also the right leg.

Dec. 1, 1916, Mangabey 54, improvement marked; feeds well; can sit up without great difficulty; will probably recover.

In the foregoing experiment the test animal received serum treatment on the fifth day after the injection of virus and two days before symptoms of the disease appeared in an incubation of seven days. The disease ran a progressive, fatal course despite four injections of serum. The control animal showed evidence of paralysis on the eighth day after infection, with slowly progressing symptoms and with subsequent improvement. This animal is alive at this writing.

Summary.—A summary of the results of the foregoing experiments is as follows:

Five of the six serum-treated animals died, a mortality of 83 per cent. Four of the six control animals died, a mortality of 66 per cent. Of the four animals that received intraspinal serum therapy before the appearance of paralysis, one received one treatment, two received two treatments and one five treatments in the preparalytic stage. In one of these, the incubation period was the same as in the control animal. In the remaining three, the incubation was shorter by one to two days than in the control animals. The duration of the disease in the serum treated animals was somewhat shorter than in the controls, varying from two to six days, whereas in the latter, the acute progressive stage was from three to eight days, indicating a greater rapidity in the spread of the disease in the central nervous system. The number of serum administrations varied from two to eight, depending on the condition of the animal. They were discontinued when the animal exhibited distinct signs of improvement, or when the paralysis had progressed to respiratory difficulty.

DISCUSSION

Experimental poliomyelitis is several times more fatal a disease than human poliomyelitis, and perhaps it is rather severe on the clinical use of untested "immune" serum to compare it with experimental use of a like serum in monkey poliomyelitis. That, however, seems to be the only method known at the present time of gaining any correct

idea of the value of this method of treatment. An effort was made in the foregoing experiments to parallel clinical conditions. Two of the animals were injected with serum on the first day of the appearance of paralysis and four from five to six days after the date of infection, but in the preparalytic stage. The test animals were controlled by six animals that received no serum therapy.

Comparison of the effects of the disease in the serum-treated animals as against the effects observed in the control animals, would incline one to the inference that, at least in the experimental disease, intraspinal injections of serum are not only of no value, but also that there may be in them an element of harm. The mechanism producing the untoward effects has not been demonstrated as yet, but it may consist in the exaggeration of the pathologic process already existing by the introduction into the subdural space of a foreign substance. Marked meningeal symptoms have been observed following the introduction of serum, both in the experimental and human disease. In some instances, the spinal fluids obtained after the injection of serum have shown distinct evidences of accentuated inflammatory reaction, as indicated by increased turbidity, due to increase of cellular elements and increase in the content of albumin and globulin.

That this meningeal reaction may have a deleterious influence on the already existing pathologic process in the cord and brain proper, is not without plausibility.

Careful comparative study of the nervous tissues of the serum treated and the control animals may indicate whether or not this is the true explanation.

FURTHER STUDIES WITH THE SCHICK TEST*

ABRAHAM ZINGHER, M.D.
Assistant Director, Research Laboratory
NEW YORK

The Schick test has found considerable favor as a reliable clinical test in showing the presence of immunity or susceptibility to diphtheria, and is being used more and more by a rapidly increasing number of physicians. The test is now employed as a routine procedure in a great many institutions, hospitals, and in the private practice of numerous physicians. Not only is the test used to indicate the immunity of the children, but it is also of great value in active immunization with diphtheria toxin-antitoxin. For this purpose the Schick test is used not only to select the susceptible individuals, but also to indicate the efficiency and the duration of the active immunity. The very reliability of the Schick test when carefully carried out, indicates that, in making the test, one should take definite precautions to use a toxin of standard strength and carefully observe the exact directions for technical details.

Occasionally, however, the interpretation of the test, especially of the pseudoreaction, is quite puzzling to some physicians. When the test is either positive or negative, there is, as a rule, no difficulty in reading the reaction. It is only with the pseudoreaction and the combined reactions that some little difficulty may be experienced unless one is guided by a knowledge of the clinical course of these false reactions.

The pseudoreaction depends on a hypersusceptibility of the tissue cells of individuals to the autolyzed protein of the diphtheria bacillus, which is present in the toxin broth used for the test. The reaction is, therefore, of the nature of a local anaphylactic response. Clinically, the pseudoreaction is distinguished from the positive reaction by its rather rapid development. It appears usually within twelve to eighteen hours, reaches its height in twenty-four hours, and fades in about three to four days, leaving only an irregular area of brownish pigmentation and generally shows no scaling. In appearance the moderate pseudoreactions at the end of twenty-four hours resemble very much the fully developed positive reactions, while the marked pseudoreactions show a considerable amount of infiltration, with a central darker reddish area, surrounded by a fainter areola, which shades off into the surrounding skin. To make a final reading of the Schick test at the end of twenty-four hours, therefore, is fraught with the danger of confusing the true with the pseudoreactions.

* Submitted for publication April 6, 1917.
* From the Research Laboratory, Department of Health.

To exclude the pseudoreactions two methods are open:

(*a*) One is to make the test and wait three to four days before the final observation. By this time the pseudoreaction generally will have faded and can be recognized by a blotchy area of pigmentation, while the true positive reaction will be at its height. The positive reaction will show at this time a definite circumscribed area of scaling redness, which gradually develops a brownish pigmentation. Those tests, however, which show only areas of bluish discoloration, or faded irregular areas of brownish pigmentation which do not scale, are generally the remains of pseudoreactions. These reactions were at their height at the end of twenty-four hours. It is important not to mistake them, when seen at the end of seventy-two hours, for faintly positive Schick tests. Where doubt exists, it is better to make a control test with heated toxin and observe the reaction at the end of twenty-four hours.

(*b*) A second method, which has certain very definite advantages, consists in using as a control on the opposite forearm at the same time the Schick test is made, a solution of diphtheria toxin which has been heated to 75 C. for five minutes.[1]

By heating the toxin broth at this temperature the soluble toxin is destroyed, while the autolyzed protein of the diphtheria bacillus, which causes the pseudoreactions, is not appreciably affected. The control test with the heated toxin will reveal the pseudoreaction and combined reactions. Observations must be made at the end of twenty-four hours, and again at the end of seventy-two or ninety-six hours. The twenty-four-hour reading will give fairly accurate results in about 95 per cent. of the tests, when the *control test* with heated toxin has also been made. If *negative,* both the test and control will be normal. If a *pseudoreaction* is present, both the test and the control will show areas of redness and infiltration, which are similar in size and appearance; both reactions will fade at the end of seventy-two hours and leave only a small irregular area of pigmentation, and generally no scaling. The pseudoreaction varies in intensity in different individuals from an area of circumscribed redness without infiltration to a reaction which shows a considerable degree of redness and infiltration, and a more or less characteristic clinical appearance.

If a *combined* reaction is present, the redness and infiltration at the site of the Schick test will be more marked at the end of twenty-four hours than in the control test. At seventy-two hours the positive reaction will be quite distinct, while the control test will show only a blotchy

1. Zingher, Abraham: The Pseudoreaction in the Schick Test and Its Control, Jour. Am. Med. Assn., 1916, **66,** 1617.

area of pigmentation representing the pseudoreaction elements of the test. If the test is *positive,* the reaction at the end of twenty-four and seventy-two hours will be positive only at the site of the Schick test. The *negative* and the *pseudoreactions* indicate immunity, the *positive* and the *combined* reactions, susceptibility to diphtheria.

The Schick test and the control test were made on all the inmates of two institutions, the New York Foundling Hospital and the Dominican Convent. In addition to noting the frequency and character of the pseudoreactions, some interesting observations were made at the first institution on certain phases of natural immunity, transmission of immunity from mother to offspring, and the duration of the passively acquired immunity in the infant.

I. OBSERVATIONS AT THE NEW YORK FOUNDLING HOSPITAL

In this institution we had opportunity not only to test some 500 children of varying ages, but also to make comparative observations on ninety-three mothers and their infants. Von Gröer and Kassowitz[2] have shown that mothers and their new-born infants reveal, as a rule, a similar antitoxin content. If present, the antitoxin in the infant's circulation is probably derived from the mother through the placenta. The immunity of the infant is temporary, lasting from four to six months.

Tables 1 to 3 give summaries of the results noted in this institution.

TABLE 1.—SUMMARY OF RESULTS WITH THE SCHICK TEST AND CONTROL TEST AT THE NEW YORK FOUNDLING HOSPITAL

	Immunes			Nonimmunes			Total Tested	Per Cent. Pseudo	Per Cent. Positive and Combined
	Negative	Pseudo	Total	Positive	Combined	Total			
Children, 0 to 8 yrs.	354	23	377	140	2	142	519	4.4	27.5
Adults.....	59	43	102	6	5	11	113	38.0	9.7
Total.....			479	...	...	153	632		

In Table 1 it is interesting to note the relatively small number of pseudoreactions in children up to 8 years of age (4.4 per cent.) and the relatively large number in adults (38.0 per cent.), as compared with the positive Schick tests, of which the children (27.5 per cent.) have nearly three times as many as the adults (9.7 per cent.).

2. Von Gröer, F., and Kassowitz, K.: Studien über die normale Diphtherieimmunität des Menschen, II. Ueber das Verhalten des normalen Diphtherieantitoxins bei Mutter und Neugeborenen, Ztschr. f. Immunitätsforsch. u. exper. Therap., 1914, Orig., *23,* 108-126.

TABLE 2.—Summary of Schick Tests by Age Groups

Age	Total	Negative	Positive	Per Cent. Pos.
0 to 6 months	101	82	19	18.0
6 to 12 months	84	40	44	52.3
1 to 2 years	52	28	24	46.1
2 to 4 years	127	82	45	35.8
4 to 6 years	108	88	20	18.5
6 to 8 years	25	22	3	12.0
Total	497	342	155	31.2

Table 2 shows that the largest proportion of positive Schick reactions was found between the ages of 6 months and 4 years. The positive reactions diminish rapidly after the fourth year of life.

TABLE 3.—Comparative Results with Schick Test in Mothers and Infants

Ages of Infants, Months	A Mother Neg. Schick Infant Neg. Schick	B Mother Neg. Schick Infant Pos. Schick	C Mother Pos. Schick Infant Pos. Schick	D Mother Pos. Schick Infant Neg. Schick
Up to 3	18	1	4	0
3 to 6	19	2	2	0
6 to 9	9	11	1	0
9 to 12	2	10	..	0
12 to 15	4	6	..	0
15 to 24	2	2	..	0
Total	54	32	7	0

In Table 3 the following interesting points may be noted:

1. The antitoxic immunity in the infant, obtained from the immune mother, lasts for about six months after birth. Column A shows that thirty-seven out of fifty-four infants, or 68.5 per cent., continued to show a negative test during the first half year of life. The negative test in the nine children between 6 and 9 months of age is probably due to a continuation of the passive immunity derived from the mother, while in the remaining eight children we are probably dealing with an early developed natural antitoxic immunity. A definite solution of this question can only be obtained by repeated Schick retests; the children who were still passively protected would lose their antitoxin in the course of a few months and then give a positive reaction, while those with an early developed natural immunity would continue to give a negative Schick test.

2. Column B shows that a large proportion of children belonging

to immune mothers has positive Schick tests after the sixth month of life. Twenty-seven out of thirty-two children between 6 and 15 months, or 86.2 per cent., gave a positive Schick test.

3. In Column C, seven children are shown who gave a positive reaction, and whose mothers also gave positive reactions. The results indicate definitely that where a mother has no immunity, none will be present in her infant if it is below 6 months of age.

4. Column D shows that no case was found in which the mother had a positive and the young infant a negative Schick test.

II. OBSERVATIONS AT THE DOMINICAN CONVENT

TABLE 4.—Summary of Results with Schick Test and Control Test at the Dominican Convent

Age	Immunes			Nonimmunes			Total Tested	Per Cent. Pseudo	Per Cent. Positive and Combined
	Negative	Pseudo	Total	Positive	Combined	Total			
4 to 6 years	29	8	37	14	1	15	52	15.4	28.4
6 to 8 years	446	14	60	6	1	7	67	20.8	10.4
8 to 10 years	13	12	25	4	3	7	32	37.5	21.8
10 to 15 years	42	25	67	2	2	4	71	35.2	5.6
Total	130	59	189	26	7	33	222	26.5	14.8

Two hundred and twenty-two children varying in age from 4 to 15 years were tested with the Schick test and the control test. Table 4 gives a summary of the results. In the lower line we see that among all the children the positive and combined reactions indicating the nonimmunes were thirty-three, or 14.8 per cent., the combined reactions representing about one-fifth of the total nonimmunes. Among the 189 immunes there were fifty-nine pseudoreactions, or a little less than one-third. The percentage of pseudoreactions among all the children tested was 26.5 per cent.; the individual age groups vary, the table showing that the pseudoreactions increase rapidly after the eighth year, and are very frequent, especially among females, after the twelfth year of life. This holds especially true for the stouter individuals, who frequently give pseudoreactions.

The relatively high proportion of pseudoreactions in older children and in adults indicates the necessity of using the control test with heated toxin. Where accurate readings are needed, especially in active immunization with toxin-antitoxin, or where the Schick test has to be read within twenty-four or forty-eight hours, the control test with heated toxin will be found of great assistance.

III. OBSERVATIONS IN OTHER INSTITUTIONS

TABLE 5.—SUMMARY OF SCHICK TESTS AT THE NEW YORK CATHOLIC PROTECTORY

Age	Total	Negative	Positive	Per Cent. Pos.
4 to 6 years	126	113	13	10.3
6 to 8 years	212	202	10	4.7
8 to 10 years	91	82	9	9.9
10 to 15 years	238	220	13	5.5
15 years up	25	24	1	4.0
Total	687	641	46	6.7

TABLE 6.—SUMMARY OF SCHICK TESTS AT THE INSTITUTE OF MERCY

Age	Total	Negative	Positive	Per Cent. Pos.
4 to 6 years	62	54	8	12.9
6 to 8 years	62	52	10	16.1
8 to 10 years	47	41	6	12.7
10 to 15 years	151	141	10	6.6
Total	322	288	34	10.5

The relatively small number of positive Schick tests in other institutions, where children ranging in age from 4 to 14 years were tested, may be seen from Tables 5 and 6. In these institutions the Schick test was made without a control. The tests were read at the end of four days, and the pseudoreactions identified by the irregular blotchy area of bluish or brownish discoloration. They are included in these tables under negative Schick reactions. Table 5 shows an average of not more than *6.7 per cent.*, and Table 6, *10.5 per cent.* of positive Schick reactions.

TABLE 7.—SUMMARY OF RESULTS WITH SCHICK TEST AT ST. JOSEPH'S INSTITUTE

Age	Immunes			Non-immunes, Positive	Total Tested	Per Cent. Pseudo	Per Cent. Positive
	Negative	Pseudo	Total				
(a) Boys							
5 to 10 years	48	0	48	7	55	0.0	12.7
10 to 15 years	103	8	111	1	112	7.1	0.9
15 to 20 years	39	11	50	1	51	21.5	1.9
Total	190	19	209	9	218	8.7	4.1
(b) Girls							
5 to 10 years	24	1	25	11	36	2.8	30.6
10 to 15 years	49	11	60	9	69	15.9	13.0
15 to 20 years	28	11	39	4	43	25.6	9.3
Total	101	23	124	24	148	16.2	15.5

Table 7 shows the results with the Schick test at St. Joseph's Institute. No control tests were made. The reactions were read at the end of four days, the pseudoreactions being differentiated from the true reactions by their clinical course and appearance. It is interesting to note that among the 218 boys not more than *4.1 per cent.* gave a positive Schick test, while 8.7 per cent. gave a pseudoreaction. Among the girls, the number of positive Schick tests (15.5 per cent.), and the number of pseudoreactions (16.2 per cent.), was much higher than among the boys.

These low percentages of nonimmunes among children over 5 years of age explain the relative infrequency of diphtheria outbreaks in many institutions. They also represent, however, an encouraging factor in greatly limiting the total number of children that would need to be actively immunized against diphtheria.

If an outbreak of diphtheria occurs in such an institution, the nonimmunes can be easily selected by the Schick test for passive immunization. A considerable saving of antitoxin can be thus effected, and the unnecessary sensitization of a large number of children, with the frequently disagreeable after-effects, avoided.

SUMMARY AND CONCLUSIONS

1. The number of pseudoreactions varies in different age groups, but is considerable after the eighth year of life.

2. The intensity of the pseudoreaction varies from a simple redness to a reaction showing marked redness and infiltration.

3. For accurate work, or where the test is to be read at the end of thirty-six to forty-eight hours, the control test with heated toxin is important.

4. The antitoxin immunity which an infant derives from its mother lasts for about six months after birth. The Schick test illustrates in a very definite way the protection against diphtheria which an infant enjoys during the first half year of life.

5. Where the mother gives a positive Schick test, her infant will also generally show a positive test during the first six months of life. Where the mother gives a pseudoreaction, the infant, if young enough, will as a rule show a negative and not a pseudoreaction. The susceptibility of the tissue cells to the bacillus protein, which gives the pseudoreactions, is not transmitted from mother to offspring.

6. The largest number of positive Schick reactions is found in children between 6 and 18 months of age. This is therefore the best time, not only to test the children, but also actively to immunize with toxin-antitoxin those who show a positive reaction.

I wish to thank Dr. Charles D. Jones for his valuable assistance in two of the institutions, and Dr. A. E. Schreibman for his cooperation in the work at the New York Foundling Hospital.

420 West End Avenue.

THE EFFECT OF UNDERNUTRITION ON MUSCULAR FORCE

A STUDY OF THE INFLUENCE OF LOW DIETS, OR THE ALLEN METHOD OF TREATMENT ON THE PHYSICAL VIGOR OF DIABETICS *

JOHN R. WILLIAMS, M.D.
ROCHESTER, N. Y.

As is now generally known, the cardinal features of the Allen method of treating diabetics are fasting, and the feeding of low diets and diets so modified as to meet the metabolic needs of the individual. While fasting and low feeding have been suggested and employed by various other workers in this field, the persistent and continued use of these dietary measures to the point of making and maintaining the patient both acid and sugar free, as employed by Allen, is a radical departure from former methods of treatment.

Among the many fears which this unique treatment has excited in the minds of both clinicians and patients is that the persistent use of the low diet would gradually and seriously weaken the patient. Untreated diabetics are accustomed to eating even larger quantities of food than are normal individuals. The diet of normal individuals of course varies widely with the age and is influenced greatly by such factors as sex, habit and occupation. Few healthy persons, however, eat less than 1,500 calories per day, many eat as much as 4,000 calories per day, and the normal range may be considered as between 2,000 and 3,000 calories. According to Lusk,[1] "the average starvation metabolism of a vigorous man at light work and weighing 70 kilograms, approximates 2,240 calories, or 32 calories per kilogram, and the maintenance requirement is between 11.1 and 14.4 per cent. above the starvation minimum. This would amount to from 2,488 to 2,562 calories, or from 35.5 to 36.6 calories per kilogram of body weight in the case of the individual just referred to." It is quite generally accepted that the healthy adult individual needs, for the proper maintenance of weight and physical vigor, about 40 calories of food per kilo of body weight, and growing children from 50 to 90 calories per kilo of body weight.

All recent studies show that few diabetics can tolerate much more than half these quantities of food. In some mild cases the patients

* Submitted for publication April 19, 1917.

1. Lusk, Graham: The Science of Nutrition, 1909, p. 210.

improve to the degree that between 2,000 and 2,500 calories can be eaten without provoking a glycosuria; in the majority of mild cases they do better, however, on diets ranging between 1,500 and 2,000 calories per day.

In advanced cases the patients are obliged to live on less food in order to remain sugar free. It is common to find patients who can tolerate not more than 1,000 calories per day, and there are numerous instances of individuals who have had to live on less (Table 1).

TABLE 1.—Food Tolerance in Diabetics

Showing total food tolerance in calories of a series of diabetic patients when discharged from the hospital, who still survive. The urine of each patient was free of both sugar and ketone bodies.

Total Calories in Diet	Number Males Over 15 Years	Number Females Over 15 Years	Children Under 15 Years	
			Males	Females
700	4	1	0	1
800	0	1	0	0
900	1	2	0	0
1000	1	2	0	0
1100	2	3	1	1
1200	4	1	1	1
1300	0	7	0	0
1400	1	3	0	0
1500	4	5	0	0
1600	1	3	2	0
1700	5	7	1	0
1800	9	0	1	0
1900	4	1	1	0
2000	4	0	0	0
2100	3	0	0	0
2200	1	0	0	0
2400	2	0	0	0
Total cases	46	36	7	3

Comment.—It will be seen that 4 males and 1 female over 15 years of age and 1 female under 15 years of age, in order to remain sugar and acid free, were compelled to live on diets approximating 700 calories. Likewise 4 males and 1 female over 15 years of age, and 1 male and 1 female under 15 years of age had dietary limitations of 1,200 calories, and so on. This table illustrates very well the caloric tolerance of diabetic patients who are favorable for treatment, and it affords a fairly reliable measure of the deprivation which they must undergo. These diets range from 5 to 40 per cent. under the supposed minimum starvation metabolism requirements.

In the minds of many clinicians the question has arisen, What effect does the persistent use of a low diet have on the physical vigor of the diabetic? The fear is often expressed that its continued use must eventually exhaust the patient. Muscular weakness is one of the commonest symptoms of the disease; therefore the influence of underfeeding is a pertinent question and worthy of consideration.

During the past year the writer has endeavored to gain some tangible evidence on this point. At the suggestion of Dr. Aleš Hrdlička,

TABLE 2.—DYNAMOMETER TESTS

Case 1522; male, aged 18. Table showing a comparison over a long period of time of the total calories in the diet, weight, urine and lung air findings with the measure of muscular force as determined by tests of grip strength.

Day of Treatment	Diet in Calories	Weight, Pounds	Strength Test, Kg.	Urine		CO_2 in Lung Air, Mm.
				Sugar, Gm.	NH_3, Gm.	
397	1,700	142½	R 36 - L 24	25	1.48	38.6
402	1,310	142½	R 37 - L 30	0	0	44.6
409	1,585	146	R 36 - L 32	0	0	40.0
415	1.585	146	R 38 - L 32	0	0	43.2
421	1,585	145	R 38 - L 30	0	0	—
430	1,585	147	R 36 - L 30	0	0	44.5
437	1,600	147	R 40 - L 32	0	0	38.7
759	1,640	142½	R 46 - L 34	0	0	45.1

COMMENT: Case 1522 presents interesting features. The patient left the hospital after a stay of twenty-one days on a diet approximating 1,800 calories. This he increased rapidly by the addition of fat to 2,500 calories. The excessive fat apparently produced a cholesterinemia and was subsequently reduced to about 1,800 calories. The patient suffered from two serious "grippe colds," which for several weeks made it necessary for him to live on a diet ranging from 600 to 1,200 calories. One of these infections immediately preceded the period covered by the data in Table 2. It will be seen that while this patient's weight remained fairly constant, he gained considerably in muscular force, although he had been on a diet averaging 1,600 calories, considerably below the figures given by Lusk for the average starvation metabolism of a man doing light work, which in this patient's case would amount to 2,080 calories. It will be noted that this patient had been under treatment and on a comparatively low diet for more than two years. At the date of the last examination, he presented the usual evidences of physical vigor observable in a young man, and these observations are confirmed by an increase in his muscular force as measured by the strength of grip which, it will be noted, is well within the normal range. There are no evident reasons for thinking that this patient has in any way suffered because of the long period of undernutrition to which he had been subjected; on the contrary, it is highly probable that a serious diabetic condition has been ameliorated and a metabolic collapse averted.

assistant curator in charge of the Division of Anthropology, United States National Museum, Washington, a Collin dynamometer was used for the purpose. With this instrument the maximum pressure which can be exerted by each hand can be determined. This test, also known as the strength of grip, is used by psychologists and anthropologists as an index of general bodily strength. According to Hrdlička,[2] adult

TABLE 3.—Dynamometer Tests

Case 1881; girl, aged 16. Table showing a comparison of the total calories in the diet, weight, urine and lung air findings with the measure of muscular force as determined by tests of grip strength.

Day of Treatment	Diet in Calories	Weight, Pounds	Strength Test, Kg.	Urine		CO_2 in Lung Air, Mm.
				Sugar, Gm.	NH_3, Gm.	
2	80	90	R 15 - L 14	....	0.57	29.5
3	205	90	R 17 - L 15	....	1.17	29.5
4	226	87½	R 16 - L 15	....	0.94	28.8
5	312	85½	R 15 - L 12	....	1.29	29.5
6	445	85½	R 16 - L 14	....	1.20	39.8
7	670	86¾	R 18 - L 17	....	0.87	36.9
8	683	86¾	R 16 - L 15	....	.....	40.4
9	874	87	R 18 - L 16	....	.....	38.0
11	814	85½	R 16 - L 16	....	.....	35.6
12	1,084	85½	R 17 - L 15	....	.....	34.9
13	1.084	85¼	R 19 - L 17	....	.....	43.4
14	1,161	85¼	R 17 - L 16	...	.....	39.6
16	1,334	85	R 21 - L 16	....	.....	37.2
22	1,696	85¾	R 30 - L 18	....	.....	41.9

Comment: Diabetes was discovered in this child three months before entering the hospital. During this period she was alternately starved and overfed. Weakness was an important symptom. After the sixth day she was required to take systematic dumbbell exercise daily, together with walks in the fresh air. The test of muscular force confirms the striking improvement in the child's physical condition.

healthy American-born whites give records ranging, for pressure in the right hand, in males, from 35 to 60; in females, from 25 to 38 kg.; for pressure in the left hand, in males, from 30 to 50; in females, from 20 to 30 kg. A healthy right-handed white man from 25 to 40 years

2. Hrdlička, Aleš: Physiological and Medical Observation Among the Indians of Southwestern United States and Northern Mexico, Bureau of American Ethnology, Bull. 34, p. 143.

of age, used to some muscular work or exercise, will press with the right hand 50 to 55, with the left hand 40 to 45 kg.; a healthy right-handed white woman between similar limits of age and with good muscular tone, can press with the right hand from 30 to 35, and with the left hand 20 to 30 kg. As age advances, the muscular force in general becomes gradually less.

The test of muscular force was made in the following manner: In each instance a Collin dynamometer was used. Tests were made in

TABLE 4.—DYNAMOMETER TESTS

Case 1517; girl, aged 17. Table showing a comparison of the total calories in the diet, body weight, urine and lung air findings, with the measure of muscular force as determined by tests of grip strength.

Day of Treatment	Diet in Calories	Weight, Pounds	Strength Test, Kg.	Urine		CO_2 in Lung Air, Mm.
				Sugar, Gm.	NH_3, Gm.	
127	990	95	R 18 - L 11	8	0.75	33.2
128	895	95	R 18 - L 14	0	0	34.9
129	895	93	R 19 - L 11	5	0.43	36.1
140	915	93	R 18 - L 12	13	0.60	40.0
142	873	93	L 19 - L 12	10	0.27	37.8
143	100	93	R 18 - L 16	0	2.24	—
144	530	94	L 21 - L 19	0	2.19	38.9
145	435	93½	R 22 - L 18	4	0.61	30.0
146	670	92	R 22 - L 17	8	0.92	38.0
147	100	93	R 22 - L 17	0	2.20	33.3
148	802	94	R 19 - L 18	0	1.80	37.8
151	712	92	.....	0	1.58	37.8
159	355	93	R 24 - L 17	0	0.58	—
161	975	91½	R 22 - L 17	0	0	41.7

COMMENT: This young woman had a serious diabetes for nearly one year before it was discovered and before treatment was instituted. It will be observed that on the 127th day of her treatment, when the observations on muscular force in her case were begun, she was well advanced. This persistent low metabolic state the writer attributes to a persistent chronic infection which was localized beneath a very expensive piece of dental bridge work, and which the parents were unwilling to have removed. In spite of her very low diet, this patient lost very little in weight and maintained to a surprising degree her physical vigor, as evidenced by the strength tests. This patient led an active outdoor life, playing tennis mildly, and indulging in other forms of recreation. Shortly after the date of the last observation, already noted, the patient abandoned the treatment, ate indiscriminately, rapidly lost in weight and strength and a few months later died. This case illustrates the fact that a patient, even on a very low diet suited to the metabolic needs of the individual, may gain in physical vigor, and that a diet in excess of these limitations may cause loss of physical strength and even death.

the morning. The spirit of competition was encouraged among patients so as to excite their best efforts. Two or three trials were made with each hand and the best effort recorded. The Collin dynamometer is graduated to read in kilograms. On the clinical charts and in the tabulations accompanying this paper, R 25-L 20 means that with the right hand the patient registered 25 kilograms, and with the left hand 20 kilograms. The dial should be held toward the palm with the little set screw between the fingers. This ensures a more accurate reading and avoids hurt to the hand. The tests, where possible, were made with the patient in a standing position, with the arms held away from the body and not supported in any manner. These precautions are

TABLE 5.—DYNAMOMETER TESTS

Case 1787; woman, aged 52. Table showing a comparison of the total calories in the diet, body weight, urine and lung air findings, with the measure of muscular force as determined by tests of grip of strength.

Day of Treatment	Diet in Calories	Weight, Pounds	Strength Test, Kg.	Urine		CO_2 in Lung Air, Mm.
				Sugar, Gm.	NH_3, Gm.	
8	55	132	R 15 - L 11	6	1.30	34.3
11	695	134	R 20 - L 16	9	1.65	37.5
19	1,233	132¾	R 17 - L 14	0	0.87	42.1
109	30	135	R 20 - L 19	..	0.71	
112	1,100	135	R 22 - L 18	..	0.61	
114	1,000	134	R 26 - L 20	3	0.90	
115	900	134	R 25 - L 19			

COMMENT: Diabetes was discovered in this patient six months before the date of the foregoing observations. The chief symptom was weakness. It will be noted that the patient had a mild acidosis when she entered the hospital. During the 115 days in which she was more or less under observation, she lived on not more than 60 per cent. of the total calories thought necessary to maintain her minimum metabolism, yet she gained noticeably in physical vigor, as is evidenced by her strength tests.

necessary for accurate results. Tests of patients who are unduly worried or after sleepless nights are of value as indicating the depressing physical effect of anxiety and dissipation, and may prove misleading unless properly interpreted. They should be used guardedly in measuring the normal muscular force of patients. This was well illustrated in one of the cases studied, a sturdy male of 57 years. This man was able repeatedly to exert a pressure of 36 kilograms with his right hand and 26 with his left hand. On the day after he was told

that his blood gave a marked positive Wassermann reaction and its significance, and after twenty-four hours of worry, the greatest pressure he could exert with his right hand was 28 kilograms and with his left, 22 kilograms.

TABLE 6.—DYNAMOMETER TESTS

Case 1680; woman aged 19. Table showing a comparison over a period of 598 days of the total calories in the diet, body weight, urine and lung air findings, with the measure of muscular force as determined by tests of grip of strength.

Day of Treatment	Diet in Calories	Weight, Pounds	Strength Test, Kg.	Urine		CO_2 in Lung Air, Mm.
				Sugar, Gm.	NH_3, Gm.	
390	140	120	R 18 - L 14	.....	0.84	44.0
523	565	103	R 10 - L 12	0	.....	35.6
526	982	104½	R 12 - L 9	0		
537	1,248	100	R 15 - L 12	Trace	.....	43.0
544	973	99¼	R 12 - L 11	Trace	.....	42.9
549	1,105	103	R 12 - L 12	Trace	0.53	43.2
557	498	99	R 12 - L 10	Trace	.....	38.5
568	1,234	100	R 14 - L 9	Trace	0.15	44.1
575	1,303	101½	R 15 - L 10	Trace	0.47	42.5
582	1,155	100	R 16 - L 11	.....	.....	44.9
587	1,436	101	R 12 - L 10	0	0.54	
594	1,350	98½	R 12 - L 9	.....	0.44	38.7
598	1,429	98½	R 15 - L 11	0	0.49	43.0

COMMENT: This case presents most unusual features. Diabetes was discovered in this young woman in May, 1915. She entered the hospital for treatment in July, 1915. After a stay of one month she went home, sugar and acid free, on a diet of about 2,000 calories. Events subsequently proved that she was being overfed on fat and this was reduced. From Nov. 1, 1915, to Jan. 1, 1917, she lived on a diet averaging under 1,000 calories; much of the time it was less than 800 calories. At one time, omitting the fat entirely from the diet served to increase her carbohydrate metabolism from 20 to 70 gm. About Dec. 1, 1916, it became almost impossible to keep her sugar free when any carbohydrate was added to the diet. The patient was readmitted to the hospital and examination showed that there was a very low tolerance for protein. When the protein intake did not exceed 30 gm. the patient could tolerate upward of 50 gm. of carbohydrate and a total of 1,400 calories, whereas 45 gm. of protein and 30 gm. of carbohydrate caused small amounts of sugar to appear in the urine. The first test of muscular force was made after the patient had been under treatment for 390 days. She apparently was then in much better physical tone than when later observations were made. It is quite probable that this state of protein irritation existed for some time before its discovery. Before the 547th day of the treatment, the patient was eating from 65 to 90 gm. of protein daily, and probably was imperfectly utilizing it. After the 547th day of treatment, the protein intake was reduced to 30 gm., or less, with a general improvement in the condition of the patient, and a marked increase in the total calories which could

be safely ingested. Is it not probable that this apparent disturbance in protein metabolism and the low intake on which the patient was compelled to live had much to do with the material lessening of her muscular force?

TABLE 7.—DYNAMOMETER TESTS

Case 1709; man, aged 33. Table showing a comparison of the total calories in the diet, body weight, urine and lung air findings, with the measure of muscular force as determined by tests of grip strength.

Day of Treatment	Diet in Calories	Weight, Pounds	Strength Test, Kg.	Urine		CO_2 in Lung Air, Mm.
				Sugar, Gm.	NH_3, Gm.	
947	458	88¼	R 14 - L 10	—	—	46.4
957	485	78¾	R 9 - L 7	—	—	40.4
964	1,410	81	R 9 - L 8	—	0.91	44.0
978	1,186	80	R 10 - L 6	1	—	39.8

COMMENT: Advanced diabetics who have a low food tolerance, who constantly exceed their metabolic limitations and who frequently show both glycosuria and ketonuria, usually become very weak and remain so. Case 1709 is a good illustration of this fact. The patient, a man, 33 years of age, began the treatment of his diabetes, June 29, 1914. In the beginning the danger of eating to the limit of tolerance was not realized, with the result that the patient was constantly fed up to or but little below that point, which was about 2,500 calories. The frequent recurrence of sugar in the urine was constantly associated with a lowering tolerance and increasing muscular weakness, so that in February, 1915, the patient was unable to eat more than 1,300 calories of food without glycosuria manifesting itself. During the summer of 1915 the patient for several weeks abandoned the diet, so that by August he had developed into a condition bordering on coma. He had a very marked acidosis, and it was with difficulty that he was made sugar and acid free. Aug. 25, 1916, his alveolar air was 21.4 mm. and he excreted in the twenty-four hours 2.57 gm. of ammonia. At this time he was very weak, indeed almost dead. Sept. 2, 1916, after being sugar and acid free for several days, and with a normal alveolar air (46.4 mm.), the first strength test was made. The patient was then 40 pounds under his usual weight and was on a diet of 458 calories. With his right hand he registered 14 kg., and 10 kg. with his left. During his stay in the hospital at this time it was evident that he could not safely tolerate more than 950 calories. He went home, however, and again began overeating to the point of having every few days a mild glycosuria and ketonuria, which he would correct by fasting. Under this plan of constant irritation he remained weak, as will be seen by the accompanying table. The first strength test was made after the patient had been under observation for 947 days, and the last test was made on the 978th day of observation. This table, unfortunately, only exhibits data of one brief hospital period, during which time he was under strict control. After two previous periods of hospital care, and following the one in which the above data were obtained, the patient relapsed into the habit of overeating, to the point of producing a mild glycosuria and ketonuria. Death finally resulted from exhaustion and coma. The career of this patient is typical, in so far as physical vigor is concerned, of the majority of patients who eat to the point of keeping their bodies in a state of metabolic exhaustion. The writer has notes on several similar cases, in all of which overeating led to a striking loss of muscular vigor, and, eventually, to exhaustion and death.

TABLE 8.—Comparison of Muscular Force as Determined by Strength of Grip with Age, Weight and Food Tolerance in a Series of Cases

Case No.	Day of Treatment	Age	Weight, Net Pounds	Weight,* per Cent., Over (+) Under (—) Normal	Minimum Normal Caloric Needs of Patient	Caloric Tolerance of Patient	Strength Test,† Kg.
Males							
1877	14	57	120½	6 +	1,740	1,846	R 28 - L 22
1686	19	50	180	20 +	2,618	1,668	R 35 - L 32
1878	17	50	192¾	11 +	2,794	1,950	R 35 - L 30
1543	36	60	142½	14 —	2,070	1,727	R 30 - L 24
1845	26	27	132	24 —	1,920	2,089	R 46 - L 38
1866	16	67	130½	20 —	1,898	1,261	R 39 - L 31
1672	18	50	167	6 +	2,429	2,194	R 37 - L 32
1536	36	50	131¼	23 —	1,907	1,858	R 42 - L 37
1729	176	48	267	57 +	3,884	1,210	R 58 - L 48
1688	287	23	133	9 —	1,932	1,800	R 45 - L 38
1522	750	20	139	6 —	2,019	1,640	R 46 - L 34
1882	16	19	118	18 —	1,715	1,778	R 32 - L 28
1681	49	10	53½	21 —	777	618	R 6 - L 6
Females							
1787	115	52	134	4 —	1,949	960	R 26 - L 20
1800	18	32	85¾	36 —	1,290	1,141	R 20 - L 15
1816	26	47	113¼	13 —	1,648	1,775	R 22 - L 16
1799	22	68	150	3 —	2,326	1,075	R 12 - L 15
1545	67	39	75¼	45 —	1,094	736	R 16 - L 14
1582	208	29	108¾	17 —	1,580	1,105	R 18 - L 15
1739	214	62	203½	31 +	2,960	1,540	R 30 - L 20
1680	558	20	98	24 —	1,424	1,429	R 15 - L 11
1507	318	20	113	12 —	1,644	955	R 17 - L 18
1567	42	20	95	25 —	1,385	1,320	R 18 - L 16
1517	161	18	87	27 —	1,264	975	R 22 - L 17
1758	28	13	69½	20 —	1,011	1,210	R 10 - L 11
1718	28	14	68	29 —	989	843	R 11 - L 6

* Determined by dividing net weight by normal weight based on sex, age and height, according to the standards of the New York Life Insurance Company.

† The minimum normal pressure exerted by healthy men between 25 and 40 years of age, according to Hrdlicka, is right hand, 35 to 60 kg.; left hand, 20 to 35 kg.; women between 25 and 40 years of age, right hand, 25 to 38 kg.; left hand, 12 to 20 kg.

Comment: Diabetics as a rule are underweight. Allen has pointed out that patients have less difficulty in keeping sugar free when they are thin than when they are fat. In the foregoing tables the weights normal and actual are compared with the evidences of muscular force as shown by the strength of grip. It will be noted that although these patients, for the most part, were thin, some of them very thin, and were living on diets much below the normal minimum requirement (32 calories per kilo of body weight), they nearly all gave quite satisfactory responses to the test of muscular force.

SUMMARY AND CONCLUSION

1. This investigation supports the common clinical observation that diabetics, as a rule, are distinctly physically weaker than normal persons. Loss of body musculature may partly explain this, but it is probable that the lessened amount of food metabolized in these cases does not provide sufficient energy for the normal exercise requirements of the body. There appears to be a direct relationship between food tolerance and muscular vigor. As food tolerance increases, so does also muscular tone. Decline in food tolerance is accompanied by loss of physical vigor.

2. The continued use of a low diet for many months, even though it fall far short of the energy requirements of the body, provided it is within the physiologic limitations of the body to metabolize it, will cause an appreciable gain in muscular tone, although the amount of physical effort that such a person may be able to put forth may be considerably below the normal. This is in accord with clinical experience that nutrition within the tolerance of the patient gives the greatest comfort, strength and sense of well being and, as Joslin has pointed out, the greatest expectation of life.

3. These observations also show that while diabetics living on a diet below normal physiologic requirements possess a diminished muscular vigor, feeding them beyond their metabolic limitations causes not only a further reduction in their tolerance for food, but also an even greater loss of strength. This is contrary to the view commonly held by both physicians and laymen. There is no justification for the common notion that overfeeding causes even a temporary increase in comfort or body strength.

The general conclusion from this inquiry is that diabetics gain in physical vigor as they become and remain sugar free, while overfeeding causes a definite and often a serious loss of strength.

Attention is called to the use of the dynamometer as a simple and fairly trustworthy method of measuring muscular tone or physical vigor. For this purpose, it has a wide range of application in the study of metabolic and other diseases, and in my hands has yielded valuable information in the study of both diabetes and nephritis.

AURICULAR FLUTTER

A CONSIDERATION OF SOME PROBLEMS ARISING IN THE STUDY OF A CASE, AND OF THE LITERATURE *

JAMES D. HEARD, M.D., AND ARTHUR E. STRAUSS, S.B., M.D.†
PITTSBURGH ST. LOUIS

Auricular flutter is that condition in which the auricles contract rhythmically and coordinately at a greatly accelerated rate, the lower limit of which has been arbitrarily placed by Lewis[1] at 200. The rate of the ventricles is usually slower than that of the auricles. This difference in rate is due to the fact that the ventricles fail to respond to every impulse originating in the auricles.

The term "auricular flutter" was first applied clinically by Jolly and Ritchie[2] in 1911; but the condition had been previously described as occurring in both humans[3] and animals.[4] Before the term was generally accepted, we find auricular flutter referred to as "jugular embryocardia," "auricular tachysystole," "auricular tachycardia," and "auricular tachyrhythmia." [5] From the time that this disturbance in mechanism had been first recorded, until 1914, when Ritchie published his book, fifty-three cases, including those of Ritchie, had been reported. This fact, especially in view of the difficulty of diagnosis, indicates that the disorder is not uncommon. It has been reported as occurring in patients from 5 to 74 years of age, and in both sexes, though it predominates in the male. Of Ritchie's cases, 85 per cent. were males. Like other disurbances, flutter may be transient or permanent; it may last during a period of only a few seconds;[6] but the tendency is toward a period of years. Its frequently transient nature, together with the absence, in some cases, of definite pathology, seems to indicate that it

* Submitted for publication April 5, 1917.

* From the Department of Medicine, University of Pittsburgh.
† R. B. Mellon Fellow in Internal Medicine.

1. Lewis, Thomas: Clinical Electrocardiography, Shaw & Co., London, 1913.
2. Jolly, W. A., and Ritchie, W. T.: Auricular Flutter and Fibrillation, Heart, 1910-1911, **2**, 177.
3. Hertz, A. F., and Goodhart, G. W.: The Speed-Limit of the Human Heart, Quart. Jour. Med., 1908-1909, **2**, 213. (Quoted by Ritchie. See Footnote 5.)
4. McWilliam, J. A.: Fibrillary Contraction of the Heart, Jour. Physiol., 1887, **8**, 296. (Quoted by Levine, Footnote 13.)
5. Ritchie, W. T.: Auricular Flutter, W. Green & Son, Edinburgh and London, 1914.
6. Parkinson, J., and Mathias, H. H.: Tachycardia of Auricular Origin and Flutter with Phasic Variation in Auricular Rate and in Conduction, Heart, 1915, **6**, 27.

may often be merely a local manifestation of toxemia. Therefore, even if no lesions be demonstrable in the auricle on postmortem examination, we need not deny the existence of flutter as a clinical entity. The general belief that there is a single point of stimulus production in the auricle has not been proved pathologically, for in no case has such a single focal lesion been recorded postmortem. We shall not discuss the etiology of flutter; we shall merely state that it has occurred during the course of such acute infections as pneumonia and diphtheria,[7] in acute "endopericarditis,"[8] during chloroform anesthesia,[5] and in chronic alcoholism and arteriosclerosis.

During the study of the case to be presented, the several problems that interested us were: (1) a consideration of the contour of the auricular deflection, the P wave; (2) the auriculoventricular conduction time, A_s–V_s interval; (3) the auricular rate; (4) a study of blood pressure; (5) vagus action; (6) the mechanism of dissociation of auricles and ventricles in flutter and fibrillation; (7) the difficulties attending diagnosis; (8) therapy. The subjects will be discussed in sequence with the results of the investigation on our own case and a review of the literature. Any conclusions based on the study of a single case must be regarded as inferential rather than as proved.

HISTORY OF CASE

History.—W. B., man, white, single, aged 50 years; admitted to the medical service of Dr. H., St. Francis Hospital, Oct. 7, 1916; discharged Jan. 9, 1917.

Chief Complaints: Weakness associated with vertigo, dyspnea, and palpitation.

Present Illness.—For two weeks the patient had been drinking heavily and not feeling well. The morning of admission to the hospital, he had started to take a walk and had gone but a short distance when he became very dyspneic, weak, and dizzy; he also had marked palpitation, and had to sit down to rest. He started for his physician's office but had to rest frequently on the way. His physician brought him immediately to the hospital.

Past History.—Measles and mumps in childhood; said to have had "typhoid fever" at 18 and 28; alveolar abscess several years prior to admission. One year prior to admission patient fractured his right elbow; infection followed and he was in a hospital two months. He had never had chorea, rheumatic fever, or tonsillitis. There was no history of scarlatina. For ten years the patient had been subject to attacks of dyspnea, occurring two or three times a year, and lasting from a few days to several weeks. During such times dyspnea was intermittent, usually present on exertion, and accompanied by palpitation. Between attacks he had the normal capacity for work without dyspnea. During attacks of dyspnea the patient experienced a general weakness, felt faint and dizzy, "light-headed," but never lost consciousness. His physician asserted that at such times his pulse was rapid, 140 to 160. The attacks usually, but not always, followed drinking bouts. No edema was ever noticed.

7. Hume, W. E.: A Polygraphic Study of Four Cases of Diphtheria with a Pathologic Examination of Three Cases, Heart, 1913-1914, **5,** 25.

8. Neuhof, S.: Auricular Flutter Accompanying Acute Endopericarditis, Med. Rec., New York, 1915, **88,** 995.

The patient had never been cyanotic. Nycturia was present for twenty years; two or three times a night for the previous two years. No history of gonorrhea or syphilis.

Occupational History.—The patient had worked in a greenhouse for several years potting plants, and had done very little heavy work, such as lifting. Formerly he worked on a farm. Habits: Tea, 0-1 cup; coffee, 1-2 cups; tobacco, formerly used to excess, but recently in moderation; alcohol, excessive use since the age of 18; periodic drinking; sprees every few weeks; eight to ten whiskies, four to five beers daily.

Family History.—Negative.

Physical Examination.—Condition on admission: pulse rate 120, patient very dyspneic and complaining of extreme weakness. After a few hours in bed the pulse rate dropped to 60, and the subjective symptoms improved. The positive and salient findings were as follows: well developed and well nourished middle aged man; poor oral hygiene; jugular pulsation prominent, no abnormal waves recognizable; a few moist râles, which later disappeared, over both lower lobes.

Heart: Not enlarged to percussion; right border 4 cm., left border 12 cm. from midsternum; supracardiac dulness 6 cm. in width; apex palpable in fifth interspace with midclavicular line, 12 cm. to left of midsternum. The heart sounds were somewhat irregular as to force and rhythm, though many seemed of equal intensity and spacing. $A_2 > P_2$, but not accentuated. A harsh blowing murmur, apparently late systolic in time, was demonstrable at the apex and also in the axilla and over the lower sternum. The auricular contractions were not audible.

The radials were moderately sclerosed; volume of pulse was full; systolic blood pressure 132, diastolic 78; no pulse deficit. Liver dulness extended to 2 cm. below the costal margin; its edge was just palpable. No edema of extremities.

Laboratory Findings.—Blood picture practically normal; urine, negative on repeated examination; blood Wassermann, October 14, anticomplementary; November 4, positive with cholesterin antigen, negative with acetone—insoluble antigen; November 30, negative with both antigens.

Course and Treatment.—After a few hours in bed, the urgent symptoms disappeared and the pulse rate dropped one-half, as above noted. On several occasions it was observed that when the patient assumed an erect posture the pulse rate was exactly doubled. No medication was given until November 1, when the patient was placed on digitalis tincture, 20 minims three times a day. Digitalis was omitted for two doses, November 6 and 7 (*vide infra*), and was then continued as before until November 17, when auricular fibrillation was established and the drug omitted. November 20, the patient had a slight attack of acute follicular tonsillitis (mixed infection), lasting three days, with rise in temperature and pulse and general malaise. The patient was confined to bed during digitalis administration and afterward until December 13. He was then permitted to get up, effort being gradually increased. There were no cardiovascular symptoms after the first few days in the hospital. On discharge, Jan. 9, 1917, the auricles were still fibrillating. The size of the heart at this time was apparently the same as on admission.

THE P DEFLECTION[9]

The contour of the auricular deflection has been the subject of controversy since the first case of flutter was studied by the electrocardio-

9. Unless otherwise stated we shall refer to the P waves in Lead II (right arm—left leg) in this discussion.

graph. Thus it has been described by various observers as upright,[10] invert,[11] or diphasic, with the primary deflection upward,[12] or downward.[13]

We believe that the auricular deflection in our case is diphasic, and that it begins with a downstroke. The auricular deflection shows an iso-electric phase in the middle of the downstroke (Fig. 1), a phase which we believe corresponds to the diastole of the auricle and separates one auricular complex from the next. This belief is based on the following reasoning: (1) In certain electrocardiograms in our series the P of Lead I is diphasic, primarily downward (Fig. 2); (2) an iso-electric phase within the limits of auricular systole is of extreme rarity. Thus, in a study of over 300 cases in our own series, of which twenty-one showed diphasism of the P wave, such a phase does not occur in a single instance. Furthermore, in only one case in

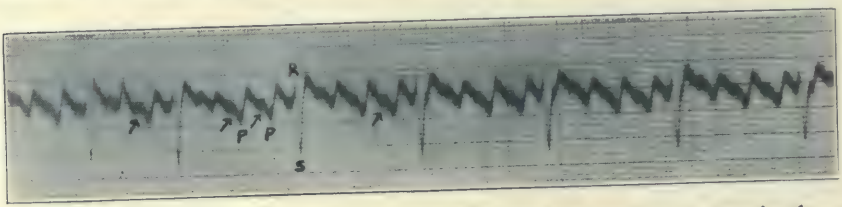

Fig. 1.—(No. 2, Lead II). Electrocardiogram showing the iso-electric phase which we believe represents auricular diastole. The P wave is diphasic, primarily downward.

The ordinates in all electrocardiograms shown represent 10^{-4} volt, the heavy and fine abscissae represent time intervals of 1/5 and 1/25 second, respectively. All figures except Figures 12, 13, and 14 are from the case described in the body of paper.

the literature have we seen such a curve, that shown by Ritchie[5] in a case of complete block following flutter, in which there is an iso-electric line in the middle of the P wave which is diphasic but primarily upward (see Ritchie's Fig. 34); (3) Lewis[10] asserts that, "the normal length of P is decidedly under 0.20 second, and if the auricular rate is fast,

10. Lewis, T.: Observations on a Curious and not Uncommon Form of Extreme Acceleration of the Auricle, "Auricular Flutter," Heart, 1912, **4,** 171. See also Ritchie, Footnote 5.

11. Parkinson, J., and Mathias, H. H.: Tachycardia of Auricular Origin and Flutter with Phasic Variation in Auricular Rate and in Conduction, Heart, 1915, **6,** 27. Rihl, J.: Hochgradige Vorhoftachysystolen mit Ueberleitungstörungen und electiver Vaguswirkung, Ztschr. f. exper. Path. u. Therap., 1911, **9,** 277 (Quoted by Lewis, Footnote 10). Lewis, T.: Observations on Disorders of the Heart's Action, Heart, 1912, **3,** 279.

12. Cohn, A. E.: Auricular Tachycardia with a Consideration of Certain Differences Between the Two Vagi, Jour. Exper. Med., 1912, **15,** 49. See also Footnote 5.

13. Levine, S., and Frothingham, C., Jr.: A Study of a Case of Auricular Flutter, THE ARCHIVES INT. MED., 1915, **16,** 818.

P is shorter than this." In our case, the duration of the auricular deflection, if the iso-electric phase be excluded, would be about 0.18 second. This is more nearly normal than 0.28 second, which would be the duration with the iso-electric line included in auricular systole. It is, in fact, so nearly normal that we do not need the added factor of a development of electric potential during auricular diastole which Lewis finds necessary to explain his theory of the contour of P. This author illustrates his point by Figure 31 of his article,[10] in which he gives 0.22 second as the duration of P. The figure shows the iso-electric line, and if this is excluded as being a manifestation of diastole, the P wave would measure between 0.11 and 0.12 second, as we should expect. Should our conception of P be generally applicable, Lewis'[10] rule, that the length of the auricular cycle in flutter is inversely and exactly proportional to the rate, would be overthrown; (4) Lewis[10] says that if the auricular rate is over 260 a minute, the P waves will be contiguous. In our case, in which the iso-electric line is so often

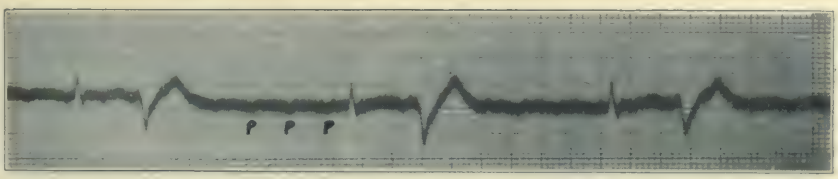

Fig. 2.—(No. 28, Lead I). Electrocardiogram showing the diphasic character of the P wave in Lead I. P is primarily downward.

prominent, the rate varies between 230 and 255, thus falling below that thought necessary for contiguity, and leaving a period for the manifestation of diastole, namely, the iso-electric phase. This latter reasoning, however, cannot be universally applicable, since such an iso-electric phase has occurred in the reported cases with rates as high as 281 (Ritchie,[5] Case 2, Figs. 47 and 81). In Jolly and Ritchie's original report on flutter,[2] the iso-electric phase is very definite with an auricular rate of 272 (their Fig. 20). Two other cases of flutter in our series, however, fail to show the iso-electric line. From the foregoing statements it is evident that there is no constant shape of P in flutter. Even all of our curves in this case do not show a definite iso-electric line.

In agreement with the general impression, we find no change in the shape of the P wave, either as a result of vagus pressure or of digitalis administration in our flutter case, although in cases in which the pacemaker is believed to be at the normal site, vagus stimulation reduces the height of P both in man[14] and in dogs.[15] Whether or

14. Robinson, G. Canby, and Draper, G.: Studies with the Electrocardiograph on the Action of the Vagus Nerve on Human Hearts. II. In Children with Chronic Valve Disease, Jour. Exper. Med., 1912, **15**, 14.

15. Goddard, C. H.: Changes in the P Wave in Human Electrocardiograms, The Archives Int. Med., 1915, **16**, 633.

not the stimulus production in flutter may originate at the normal pacemaker, is still uncertain, but the mass of evidence is in favor of an ectopic origin.

A_s–V_s INTERVAL

The determination of the conduction time in flutter has been of interest because of the great rapidity of auricular rate, which makes it difficult to determine to which auricular stimulus the succeeding ventricular complex corresponds. After measuring the P–R intervals in many curves, Lewis decided that the ventricle responds not to the auricular beat immediately preceding, but to the second one before it. This has been our guide in the measurement of the A_s–V_s interval, and on these measurements we base our conclusions.

We found a great variation in the length of this interval, which we believe to be due, not to the occasional indistinctness of the beginning of the P waves, but to other factors little understood at present. The

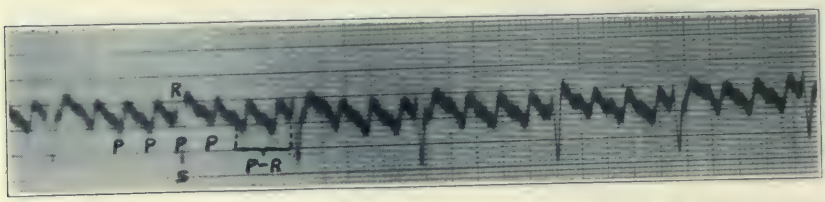

Fig. 3.—(No. 1, Lead II). Electrocardiogram taken Oct. 12, 1916, before administration of digitalis. The P-R intervals are 0.48, 0.44, 0.41, 0.48, 0.42, 0.42 second, reading from left to right. Note absence of relationship between P-R intervals and degree of block or length of preceding pauses (R-R intervals). The P-R intervals are measured from the beginning of the downstroke of P (following the iso-electric phase) to the beginning of the R wave.

same differences are seen if we consider the P wave as diphasic, upright, or invert, and take corresponding points for our measurements. Thus, in our first plate (Fig. 3), we find a variation in the P–R interval of 0.07 second, our measurements for one lead being 0.48; 0.44; 0.41; 0.48; 0.42; 0.42 second. Lewis,[10] Fulton,[16] and others state that the A_s–V_s interval varies with different degrees of block, there being a shorter conduction time following a long pause, and a longer P–R interval following a short pause. That the variation noted in our case is not due to this factor is made clear by measuring the preceding pauses (R–R intervals). Likewise, in our other curves of the case, we find no constant relationship between the degree of block and the conduction time.

16. Fulton, F. T.: Auricular Flutter with a Report of Two Cases, THE ARCHIVES INT. MED., 1913, **12**, 475.

Cohn and Lewis,[17] in experiments on dogs, in which the auricles are kept at a constant rate by electrical shocks, find that stimulation of the left vagus prolongs conduction time more than does stimulation of the right. In general we find, where the same degree of block is produced by right and left vagus stimulation, that the P–R interval is slightly longer with left vagus stimulation than with right, but that the difference is no greater than that occurring spontaneously, and our series is too small to allow any definite conclusions to be drawn. We can only say that the results are suggestive of confirmation of the experimental work done in animals.

Digitalis is supposed to exert its beneficial action partly by causing prolongation of the P–R interval, and by increasing the degree of block. Later in this paper we shall discuss the increase in block due to digitalis. We are at present interested in its effect on the conduction time. In Plate 25, Lead III (Fig. 4), taken after 460 minims of tincture of digitalis had been given, if we measure the P-S interval (which

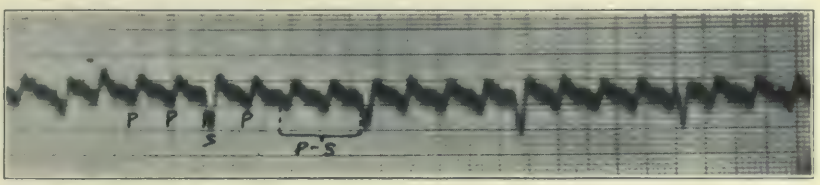

Fig. 4.—(No. 25, Lead III). Electrocardiogram taken after administration of 460 minims of tincture of digitalis over a period of nine days, showing prolongation of the conduction time (P-S interval). The iso-electric phase of the auricular deflection is well shown.

corresponds to the P-R interval of Lead II) from the P immediately preceding the ventricular complex, we find that it varies from 0 to 0.08 second; or, if we take the case where the S wave begins on the iso-electric line, the interval in that instance would be 0.28 second. Measuring from the next preceding P, we find a variation from 0.32 to 0.34 second, or, in the one case, 0.54 second. In 4-1 block before digitalis was begun the P-R interval was 0.41 to 0.48 second. It is a well-known fact that during normal mechanism digitalis may prolong the conduction time, and it would be unusual for the drug to act in the opposite manner in flutter. However, if the third preceding P wave is taken as the stimulus that causes the ventricle to contract, we get a measured A_s-V_s interval of 0.54 to 0.60 second, which agrees with the prolongation seen in normal mechanism as a result of digitalis administration. This is, with little doubt, the conduction time in this case.

17. Cohn, A. E., and Lewis, T.: Predominant Influence of Left Vagus Nerve on Conduction Between Auricle and Ventricle in Dogs, Jour. Exper. Med., 1913, **18**, 739.

AURICULAR RATE

The rate of the auricle in the individual case of flutter usually tends to remain the same under varying conditions and at different times, unaffected by postural changes or nervous influences.[16] However, we believe that too much stress has been laid on this aspect of flutter. Indeed, many instances are cited in which a distinct change in rate has been noted. Lewis in his monograph gives several examples; White[18] notes a difference of 44 in the rate at different times; Parkinson and Mathias,[6] in their unique case, note a gradual change from 240 to 200 during the flutter period. Our case shows a variation from 230 to 255. The changes are apparently spontaneous, however, not occurring in definite relation to those influences that are normally supposed to affect the heart rate, although the slight slowing produced by deep breathing observed by Levine and Frothingham[13] was attributed by them to vagus effect, and the change in auricular rate in the case of Parkinson and Mathias was also believed to be due to nervous influences.

In our case, the auricular rate became somewhat slower during full digitalization. Whether this result was an effect of the digitalis, or merely coincidental, cannot be said with certainty.

The rate of stimulus production in fibrillation is increased over that in flutter, and as a result the ventricles usually beat more slowly when the change from flutter to fibrillation occurs. This effect may be due partly to the fact, experimentally determined, that acceleration of the auricles in the presence of slight grades of block tends to a reduction of the ventricular rate;[10] but it may be due also in part to the fact that many of the auricular stimuli in fibrillation have not the minimum threshold value necessary either for conduction through the junctional tissues or for excitation of response of the ventricular musculature itself.

BLOOD PRESSURE

Very little careful study has been made of the correlation of blood pressure during flutter and fibrillation in a given case. Ritchie[5] says that in flutter a systolic blood pressure as high as 260 to 275 mm. of mercury has been recorded, and he believes that the age incidence suggests some relationship between arteriosclerosis and flutter. Levine and Frothingham[13] made a study of the blood pressure in their case and noted a decrease in pulse pressure during the normal period as compared with that during the period of flutter.

We began our investigations of blood pressure during the period of flutter and hoped to be able to compare the three phases of flutter, fibrillation, and normal mechanism. At the time of writing, however

18. White, P. D.: A Study of Auriculoventricular Rhythm Following Auricular Flutter, THE ARCHIVES INT. MED., 1915, **16**, 517.

(March, 1917), the case is still in fibrillation. We can, therefore, present our findings for only the first two phases. All the blood pressure readings were taken by one of us (S), who assumes individual responsibility for this portion of the article. The pressures were all taken under approximately the same conditions: with the patient in bed continually until December 13; from the 13th to the 19th, inclusive, with the patient lying in bed, although he was up part of each day; all thereafter, with the patient sitting up and out of bed during the whole day.

The "average systolic" blood pressure was taken according to the method of James and Hart.[19]

The force of the pulse during flutter was nearly constant over long periods of time; so it was not thought necessary to take an average systolic reading, although that course might have been advisable because of an occasional relative pulse deficit. During the period of fibrillation it was noted, with some surprise, that the point at which the first systolic sound was heard over the brachial artery on lowering the pressure in the cuff, after the pulse had been obliterated, varied within such narrow limits that we felt justified in using that point as an index to the systolic reading. The same observation was made regarding the point marking the change from the loud, clear sound of the third phase to the muffled, low sound of the fourth phase, which was called the diastolic pressure.[20] To obtain such results, however, the pressure changes in the cuff must be made slowly when approaching these points.

The accompanying table (Table 1) will show our readings during the study, the summary of which follows (Table 2).

Despite the great daily variation in pressure, there was nothing in the patient's general condition to indicate such change. There was a definite fall in pulse pressure during the change from flutter to fibrillation, and if we take the "average systolic" as indicative of the true pressure in fibrillation, the fall in systolic pressure was very marked. It would seem that with such a fall there would be some change in the condition of the patient; yet none was noticeable and the patient was aware of no change.

In this case, the daily variation of the "average systolic" blood pressure was almost as great as that of the systolic pressure taken in the usual way. This observation threw some doubt on the value of the

19. James, W. B., and Hart, T. S.: Auricular Fibrillation: Clinical Observations on Pulse Deficit, Digitalis, and Blood Pressure, Am. Jour. Med. Sc., 1914, **147,** 63.

20. Warfield, L. M.: Studies in Auscultatory Blood Pressure Phenomena. The Clinical Determination of Diastolic Pressure, Jour. Am. Med. Assn., 1913, **61,** 1254.

TABLE 1.—Blood Pressure

Mechanism*	Date	Systolic	Diastolic	Pulse Pressure	Average Systolic
Flutter	10/12/16	132–128	78–68	54–60	...
Flutter	10/20/16	132	80	52	...
Flutter	10/23/16	128	76	52	...
Flutter	11/ 4/16	110	65	45	...
Flutter	11/ 6/16	118	65	53	...
Flutter	11/ 9/16	135	75	70	...
Flutter	11/10/16	115	70	45	...
Flutter	11/14/16	138	60	78	...
Fibrillation	11/17/16	110†	60‡	50	70
Fibrillation	11/18/16	107–105	70–60	37–45	93
Fibrillation	11/19/16	150–140	80–65	70–75	105
Fibrillation	11/20/16	.....	.....	.....	83
Fibrillation	11/22/16	105	60	45	98
Fibrillation	11/23/16	120–115	75	45–40	111
Fibrillation	11/25/16	118–110	75–65	43–45	108
Fibrillation	11/26/16	110	60	50	97
Fibrillation	11/27/16	112	62	50	105
Fibrillation	11/29/16	112	74	38	102
Fibrillation	11/30/16	115–112	70–65	45–47	90
Fibrillation	12/ 2/16	112–110	62–60	50–50	96
Fibrillation	12/ 5/16	118	74	44	110
Fibrillation	12/ 8/16	110	65	45	91
Fibrillation	12/11/16	112	75	37	100
Fibrillation	12/13/16	130	80	50	109
Fibrillation	12/15/16	110	80	30	98
Fibrillation	12/19/16§	114	74	40	98
Fibrillation	12/27/16	80– 75	50–45	30–30	84
Fibrillation	12/29/16	90	60	30	85
Fibrillation	1/ 2/17	.....	.....	.....	99
Fibrillation	1/ 6/17	107	60	47	107
Fibrillation	1/ 9/17	120	72	48	111
Fibrillation	1/12/17	128	80	48	119

TABLE 2.—Summary of Readings Presented in Table 1

Mechanism and Posture of Patient	Systolic Min.	Systolic Max.	Diastolic Min.	Diastolic Max.	Pulse Pressure Min.	Pulse Pressure Max.	"Avg. Syst."
Flutter—lying in bed	110	138	60	80	48	78	.....
Average	126		72		56		.....
Fibrillation—patient lying in bed	105	150	60	80	37	75	70–111
Average	115		67		47		98
Patient up part of day; pressure taken lying in bed	110	130	74	80	30	50	98–109
Average	118		78		40		101
Patient up all day; pressure taken with patient sitting up	75	128	45	80	30	48	84–119
Average	100		61		39		101
Fibrillation—All above postures combined	75	150	45	80	30	75	70–119
Average	111		68		42		100

* Mechanism determined by electrocardiogram.

† During fibrillation, first sound heard with stethoscope over brachial called systolic.

‡ During fibrillation, the change from the loud, clear sound of the third phase to the muffled, low sound of the fourth phase called diastolic.

§ Pressure taken with patient in bed up to this date; thereafter with patient up.

"average systolic" reading, which though not difficult, is nevertheless time-consuming and a tax on the patience of physician and patient alike.

There was a marked constancy in the diastolic pressure during both flutter and fibrillation, with no change noted in the transition from one to the other.

While no conclusions can be drawn from the study of this single case, similar observations on other cases would be of value.

VAGUS EFFECT

As contrasted with the studies of blood pressure, observations on the effects of vagus stimulation in flutter and its allied conditions are many and they rest both on experimental work and on clinical observation. Cohn[21] gives an excellent chronological summary of the important work on the vagus. Czermak, in 1865, first described the method of stimulation of the vagus by pressure over the carotid artery in the neck; we believe this to be the method of choice in man. More recently, 1908, Aschner[22] described the oculo-cardiac reflex by which vagus effects may be obtained by pressure on the eyeball. Both methods were used in our case. In a series of tests during both flutter and fibrillation we obtained better results by pressure over the carotid than on the eyeball, although several investigators[23] have found the latter method more reliable. Levine[22] says that pressure over the eyeball does not cause pain; but in the case of no patient have we found this statement verified.

During flutter we could obtain ventricular standstill or definite slowing by pressure over right or left carotid or on either eyeball; the most pronounced effect was obtained by the Czermak method, and on the right side more than on the left (Figs. 5 and 6). An interesting exception occurred when, on one occasion, by left vagus pressure we obtained a ventricular standstill of 9.2 seconds. During this time the patient momentarily lost consciousness and showed the beginning of tonic and clonic movements of arm, thus causing the writing pen of the radial tambour to leave the tracing paper (Fig. 7). The patient, when asked to describe his feelings afterward, said that he "felt light-headed and dozed off." We believe that by vagus pressure in this instance we produced an artificial Stokes-Adams syndrome. There-

21. Cohn, A. E.: Difference in Effects of Stimulation of the Two Vagi on Rate and Conduction in the Dog's Heart, Jour. Exper. Med., 1912, **16,** 732. See also Footnote 12.

22. See Levine, S.: The Ocular Reflex, an Electrocardiographic Study with Special Reference to the Differences Between R. and L. Vagal and Ocular Pressures in Tabetics and Non-tabetics, THE ARCHIVES INT. MED., 1915, **15,** 758.

23. Ferralis, G. V., and Pezzi, C.: Reflexe oculo-cardiaque et extrasystoles, Arch. d. mal. du cœur, Paris, January, 1916, **9,** 1; abstr. Jour. Am. Med. Assn., 1916, **66,** 924. See also Footnote 13.

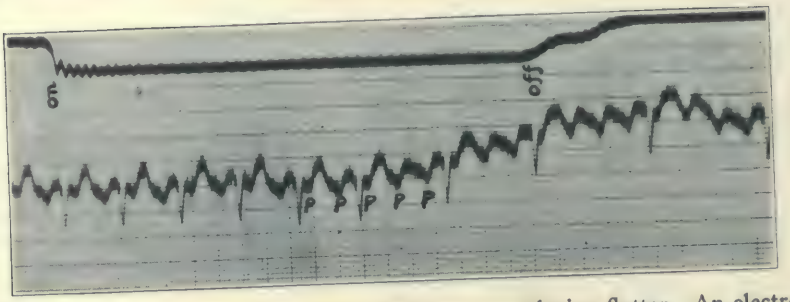

Fig. 5.—(No. 12, Lead II). Left carotid pressure during flutter. An electrocardiogram showing increase in degree of block due to vagus stimulation. Note latent period before effects of pressure become evident and residual action after pressure is released. Upper line is signal showing duration of pressure.

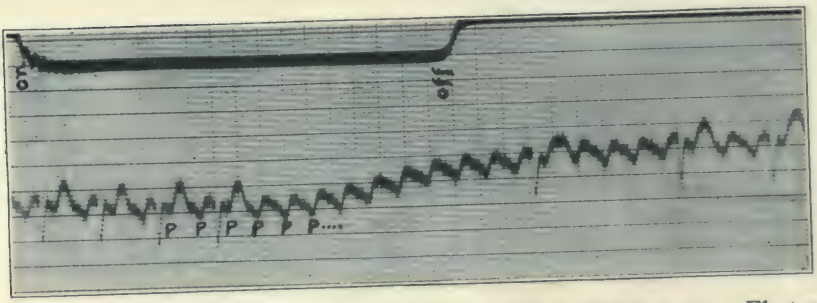

Fig. 6.—(No. 13, Lead II). Right carotid pressure during flutter. Electrocardiogram showing 11-1 block as a result of right vagus stimulation. Before pressure there was a regular 2-1 block. During pressure the auricles continue to beat as before. Latent period and residual effect are evident.

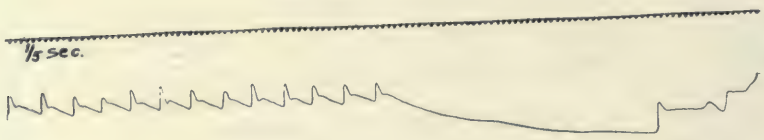

Fig. 7.—Tracing from left radial artery showing effect of pressure over left carotid. During the period of ventricular asystole, which lasted more than nine seconds, the patient experienced an artificial Stokes-Adams syndrome. Each division of time-marker represents ⅕ second. Tracing made before administration of digitalis. (Fig. 7 retraced.)

after, because of danger to the patient, we never produced sufficient pressure to cause such a prolonged period of asystole. With much shorter periods of asystole, however, the patient said he felt "light-headed" as during the attacks of dyspnea and weakness described in the case history.

There was always a latent period between the onset of pressure and the first effect, but the time of this could not be accurately determined because of the uncertainty of the method employed, the onset of stimulation not being synchronous with onset of pressure on the neck. Robinson and Draper[24] mention this uncertainty of time of onset as

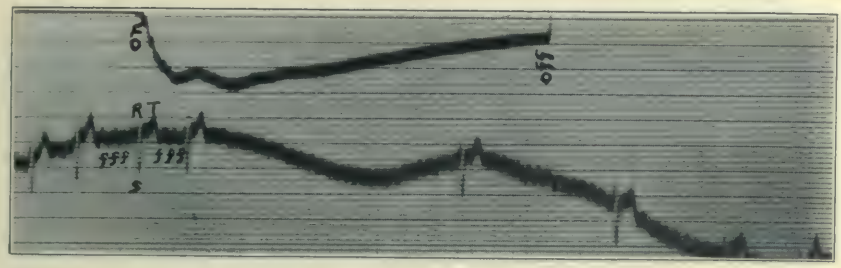

Fig. 8.—(No. 59, Lead II). Right carotid pressure during auricular fibrillation. The longest period of ventricular asystole (R-R interval) was 4.1 seconds. The plate was moving more slowly than in preceding figures. The abscissae, although indistinct in the prints, are clearly shown in the original photographic plates. The upper line is a signal showing duration of pressure.

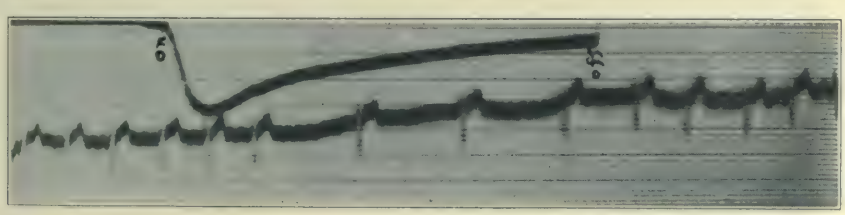

Fig. 9.—(No. 60, Lead II). Left carotid pressure during auricular fibrillation. Note legend of Figure 5.

one of the disadvantages of this method of vagus stimulation and assert that others are the uncertainty of result, the impossibility of measuring the strength and duration of the stimulus, and the danger to the patient. In their experiments they observed no ill effects, only one case showing transient vertigo, but our observation of loss of consciousness as a result of long asystole warned us that the method is not without danger. After pressure was released, the effects of vagus stimulation continued for some time.

24. Robinson, G. Canby, and Draper, G.: Studies with Electrocardiograph on the Action of the Vagus on Human Hearts. I. Effect of Mechanical Stimulation of the Vagus Nerve, Jour. Exper. Med., 1911, **14**, 217.

During stimulation by carotid pressure, there was an occasional tendency toward ectopic beat formation such as noted in eyeball pressure;[25] otherwise no change occurred in the ventricular complex of the electrocardiogram, and the auricles were entirely unaffected as to rate or form, a fact already noted by all investigators who have studied this aspect of the question. This is further evidence of the ectopic origin of stimulus production in flutter, for in normal hearts in both man[14] and animal[17] the auricles are under vagus control — the right vagus with greater control over the site of stimulus production, the left with preponderant action on the conduction tissues.[26]

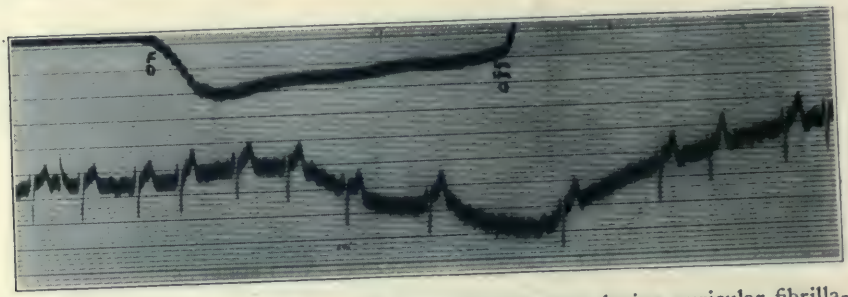

Fig. 10.—(No. 61, Lead II). Right ocular pressure during auricular fibrillation. Note legend of Figure 5.

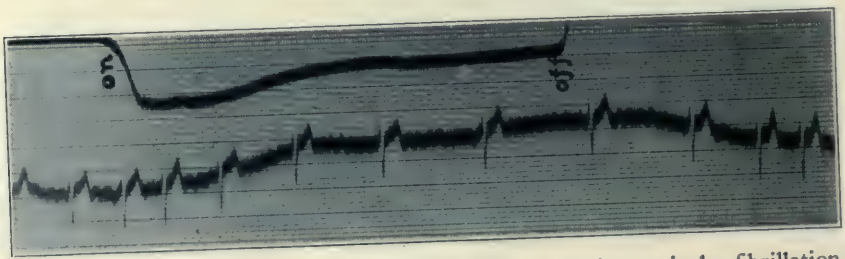

Fig. 11.—(No. 61, Lead II). Left ocular pressure during auricular fibrillation. Note legend of Figure 5.

This effect, though the rule, has its exceptions, noted both clinically and in experimental animals; thus Cohn,[21] in two out of fifty-four experiments, finds the opposite action from that expected. Robinson and Draper[14] find right and left vagi acting alike in one case and contrary to rule in another. White,[18] in his flutter case, finds the right vagus more effective in increasing block than the left, a result similar

25. Ferralis, G. V., and Pezzi, C.: Reflesso oculocardiaco e extrasistoli, Policlinico, Rome, 1916, **23,** Med. Sect., p. 129; Abstr. Jour. Am. Med. Assn., 1916, **66,** 2129.

26. See Footnotes 12, 14, 17, 21, and 24, and Cohn, A. E.: Effect of Morphin on the Mechanism of the Dog's Heart after Removal of One Vagus Nerve, Jour. Exper. Med., 1913, **18,** 715.

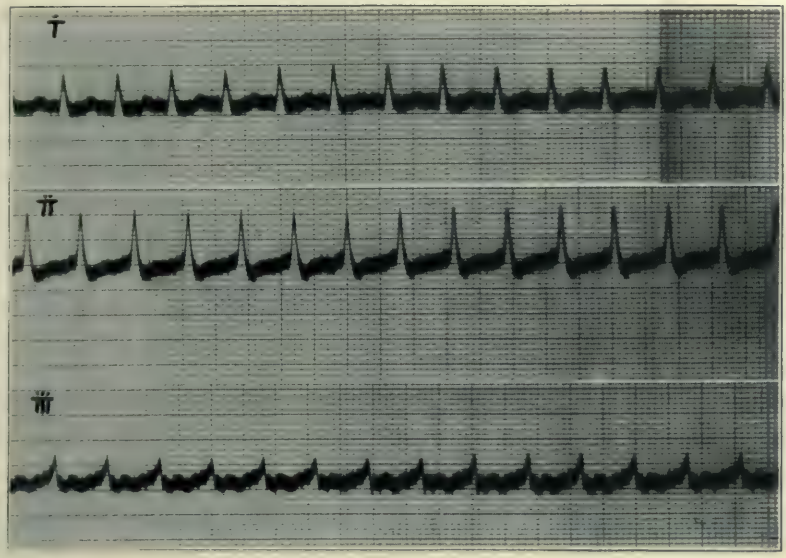

Fig. 12.—(A 321, No. 2, Leads I, II, III). Electrocardiogram taken during period of regular 2-1 block in a case of auricular flutter showing difficulties of diagnosis sometimes experienced despite graphic methods. Auricular rate 375; ventricular rate 187.5. Same case as Figures 13 and 14.

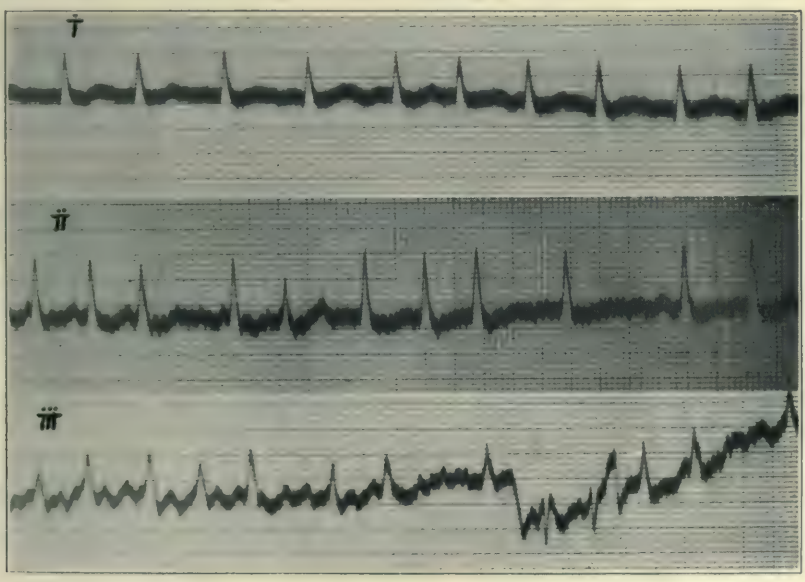

Fig. 13.—(A 321, No. 6, Leads I, II, and III). Electrocardiogram taken during period of irregular ventricular response in auricular flutter, showing close resemblance to auricular fibrillation. The latter part of Lead III is distorted by body movements of the patient. Same case as Figures 12 and 14.

to ours. Lewis[10] says that both vagi act alike, suggesting "control of the junctional tissues in man by both vagi and failing to substantiate the view of preponderance of one over the other." Ritchie[5] likewise says in reference to the selective action of the two vagi in animals that "it is doubtful whether this holds good with the human heart." Robinson and Draper,[14] however, after a series of experiments on man arrive at the conclusion that "in healthy as well as in diseased hearts the control of rate of the heart beat predominates in the right vagus and the control of stimulus conduction preponderates in the left vagus, not because of any specific activity in the nerves themselves, but, as Dr. A. E. Cohn has suggested to us, on account of a possible difference in the anatomic distribution of the two nerves." This conclusion seems to be borne out by a clinical study since made,[27] although it is only a quantitative and not a qualitative difference, and cannot be taken as an absolute rule, because of frequent exceptions.

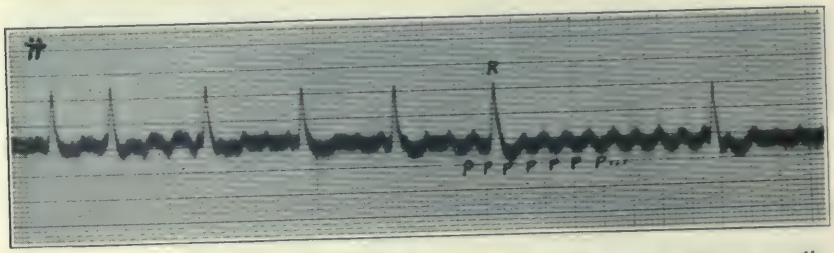

Fig. 14.—(A 321, No. 8, Lead II). Pressure over left carotid. Electrocardiogram of same case as that pictured in Figures 12 and 13, showing the value of vagus pressure as an aid to diagnosis in auricular flutter. Pressure was exerted throughout the entire portion shown. Auricular rate 375. During the long diastolic pauses the P waves are prominent. Picture taken immediately after that shown in Figure 13.

After the change in mechanism in our case, we repeated the experiments with the auricles in fibrillation, with approximately the same result as seen in flutter (Figs. 8, 9, 10 and 11).

Robinson and Draper,[24] working on normal hearts in man, noted that with R vagus stimulation the maximum pause initiated the onset of slowing, while with L vagus stimulation the maximum pause was delayed. In neither flutter nor fibrillation did we find any constancy in such effects, either by eyeball or carotid pressure.

The value of vagus pressure as a diagnostic aid in the interpretation of questionable electrocardiograms was brought forcibly to our attention in another patient with flutter who entered the hospital while this paper was being written. In this case (as yet unpublished), the auricular rate was 375, and the ventricular 187.5. From the electrocardio-

27. Cohn, A. E., and Fraser, F. R.: Paroxysmal Tachycardia and the Effect of Stimulation of the Vagus Nerves by Pressure, Heart, 1913, **5**, 93.

grams taken during regular 2-1 and irregular degrees of block, a positive diagnosis of flutter could not be made. However, with pressure over the carotid, the block was increased; the auricles continued to beat as before while the ventricles were slowed, and the electrocardiogram then showed the typical curve of flutter, making diagnosis easy (Figs. 12, 13 and 14).

THE MECHANISM OF AURICULO-VENTRICULAR DISSOCIATION IN FLUTTER AND FIBRILLATION

Mention has already been made of the fact that in auricular flutter the ventricles seldom keep pace with the auricles, there being usually some degree of dissociation between them. The generally accepted view of this dissociation is that the impulses arising in the auricle are "blocked" in the auriculo-ventricular conduction tissue, and thus fail to reach the ventricles. If there is an actual blocking of the impulses in the junctional tissues, the question arises why, in the return to normal mechanism, there is frequently no conduction defect (prolongation of A_s-V_s interval)? If we deny the presence of auriculo-ventricular block, we must in some way account for the dissociation. Is it due to fatigue of the junctional tissues or the ventricular muscles so that they will not respond to every stimulus? This causation seems improbable, because we often get more rapid contraction than is shown in flutter with 2-1 and 4-1 block without any evidence of fatigue in either conduction tissue or musculature. Lewis[10] believes that there is a primary deficiency of conduction in cases exhibiting block, because the junctional tissues have been shown capable of conducting impulses at the rate of 290 to 300 per minute, while in block, conduction is much less frequent. The longer A_s-V_s interval following a short pause and the shorter conduction time after a long pause, noted by other observers, is evidence in favor of the defect being in the junctional tissues rather than elsewhere, but we believe a factor that has been too little considered is the refractory period of muscle.

Foster,[28] as early as 1872, made the observation that weak, interrupted currents inhibit the heart in diastole. Since that time physiologists have repeatedly confirmed this observation. Carlson[29] asserts that it is not even necessary to have very rapid stimulation to produce this effect; that two or three shocks per second induce diastolic standstill in the hearts of some animals. We know, then, that heart muscle shows a prolongation of refractory period under frequently repeated

28. Foster: Pflüger's Arch. f. ges. Physiol., 1872, **5,** 191 (Quoted by Carlson, Footnote 29).

29. Carlson, A. J.: The Nature of the Inhibition of the Heart on Direct Stimulation with a Tetanizing Current, Ztschr. f. allg. Physiol., 1907, **6,** Parts 3 and 4.

stimulation. It should make no difference whether the stimulus is artificial, like that produced by repeated induction shocks applied to ventricle, or whether it comes through the usual channels from the auricle. In flutter the auricles are beating more than 200 per minute, while in fibrillation the rate of stimulus production is even more rapid, so that if these rapidly repeated impulses reach the ventricles they may cause a prolongation of the refractory period of the ventricular musculature, and in that manner produce dissociation of auricles and ventricles, dissociation usually attributed to auriculo-ventricular "block."

DIAGNOSIS

To quote from Ritchie:[5]

> Whenever a patient complains of sudden attacks of palpitation and dyspnea, with or without precordial pain, syncope, or other symptoms, and the pulse rate during the attack attains or exceeds 130 to 140 per minute, auricular flutter should be suspected. If the pulse during the attack is absolutely rhythmic, the condition is probably due to flutter. Moreover, if the attack of rhythmic tachycardia comes on suddenly and either ends abruptly, or the rate of the rhythmic pulse beats falls one-half, while the patient is taking digitalis, the auricles are almost certainly in flutter.

This statement does not cover the entire field, since, with the exception of the implied digitalis action in flutter, it would apply equally well to paroxysmal tachycardia — a disturbance of mechanism, which is not fully mentioned by Ritchie in the discussion of diagnosis, inasmuch as he only mentions that tachycardia arising in the junctional tissues, and not that arising in either auricle or ventricle. It is worthy of note that Lewis[10] states that one should suspect flutter if sinus arrhythmia fails to appear with forced respiration, or if, on the other hand, slight exercise results in a sudden doubling of rate. While recognizing the importance of clinical observation, however, one must, nevertheless, admit that definite diagnosis of flutter is made possible only by resort to graphic methods. The most valuable graphic records are those obtained by the use of the Mackenzie polygraph and the electrocardiograph. A diagnosis is also made possible by the use of the fluoroscope.[30] However, fluoroscopy is of less value than the use of polygram or electrocardiogram, the electrocardiographic study being always the method of choice. A routine electrocardiogram should be taken on every patient entering the hospital, as otherwise many cases of flutter will be missed. The importance of this routine is emphasized by the fact that a flutter patient may present a normal pulse rate of regular rhythm, while, on the other hand, varying degrees of block may result in an irregularity of rhythm which may closely simulate auricular fibrillation.

30. Holmes, G. W., and White, P. D.: Auricular Flutter Detected by the Fluoroscope, Jour. Am. Med. Assn., 1917, **68,** 844.

Electrocardiographic examination should not be limited to routine on admission, it should also be resorted to during course of treatment in order that one may note untoward effects of digitalis action, and the change of mechanism to fibrillation. That onset of fibrillation may not be recognized readily is shown by the fact that five members of the medical staff failed to note change in mechanism in this case at a time when onset of fibrillation had been shown by the electrocardiogram. It is worthy of note that during certain periods of fibrillation the pulse seemed to be less grossly irregular than during flutter with alteration in degree of block.

A combination of flutter and fibrillation, such as has been noted by Robinson,[31] was not shown on any of our records.

THERAPY

The therapy indicated in auricular flutter is to endeavor to restore normal mechanism through the administration of digitalis. This change in mechanism is not direct; there usually occurs an interval period of auricular fibrillation.

If rate of ventricle is within normal limits and the circulation is well maintained, there is no indication for drug therapy. Thus in our patient the pulse rate fell to 60 shortly after admission, and remained between 60 and 80 as long as the patient remained in bed. During this period no digitalis was given. On slight increase of effort, however, it was found that there resulted an exact doubling of rate. After we had repeatedly observed this acceleration, we decided to begin digitalis, because the increased rate was higher than normal on the lowest plane of effort on which the patient could possibly live after leaving the hospital, and, consequently, continued proper maintenance of the circulation became doubtful. November 1, we began the administration of tincture of digitalis, 20 minims three times a day. After only 100 minims had been taken, the electrocardiogram showed periods of 3-1, 4-1 and 5-1 block, the latter being the highest degree of block noted up to that time, except under artificial vagus stimulation. November 4 (20 minims tincture of digitalis having been taken since November 1), the electrocardiogram showed distinct coupling with varying periods of block — 2-1, 5-1. November 6 (320 minims taken), coupling was more pronounced and digitalis was omitted for two doses, then continued in the same dosage as before. On the 9th, there were long diastolic pauses, periods of 7-1 and 8-1 block, and coupling was so marked that we considered omitting the digitalis. Inasmuch as we had

31. Robinson, G. Canby: Relation of Auricular Activity Following Faradization of Dog's Auricle to Abnormal Auricular Activity in Man, Jour. Exper. Med., 1913, **28,** 705.

not yet obtained the result for which we were striving, we decided to continue the drug under careful observation (Figs. 15 and 16). This course was followed until November 17, at which time the auricles began to fibrillate and the digitalis was discontinued (Fig. 17). A total of 940 minims (62.6 gm.) of the tincture had been taken over the period of seventeen days since treatment had been instituted. Except for the coupling and increased degree of block, there was at no time evidence of digitalis poisoning.

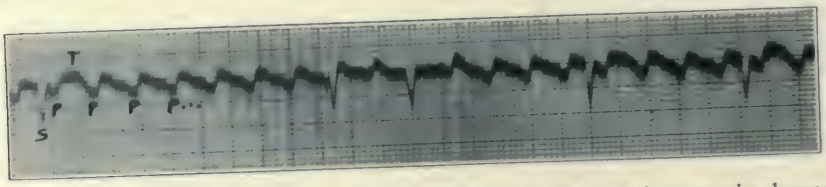

Fig. 15.—(No. 26, Lead II). Electrocardiogram showing increase in degree of block caused by digitalis. Taken after 460 minims tincture of digitalis had been given over a period of nine days. Note irregular ventricular response including 8-1 block.

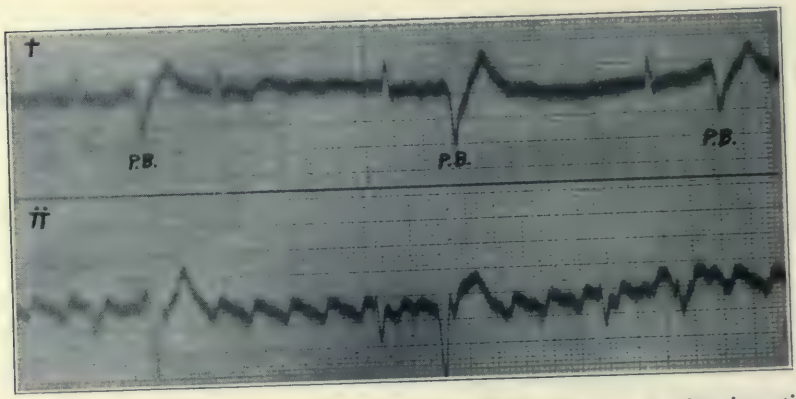

Fig. 16.—(No. 31, Leads I and II). Electrocardiogram taken after ingestion of 760 minims tincture of digitalis during a period of fourteen days. Marked digitalis coupling shown.

Of the fifty-three cases reported by Ritchie,[5] only two had received larger doses than our patient, one receiving 1,455 minims in thirty-one days, the other 1,080 minims in eighteen days. Lewis[10] reported two patients who received, respectively, 915 and 920 minims of tincture strophanthus (Cases 2 and 4). However, in each of these cases, the drug was discontinued because of diarrhea, and because, as Lewis says, there seemed no further prospect of producing auricular fibrillation. Each of these patients had been given, in a previous course, another member of the digitalis group, the drug having been stopped on account of nausea. Neühof[8] makes the statement, evidently without sufficient

proof, that the cases of flutter in which digitalis produces auricular fibrillation, later followed by normal rhythm, are those with marked decompensation. He says further, that since no decompensation was present in his case, he could scarcely have expected benefit from the digitalis. On this false premise he stopped the administration of digitalis when 10 drams had been given because "it was assumed that any further attempt to produce auricular fibrillation would be futile." Tallman[32] emphasizes the importance of large doses and asserts that we must often give digitalis to the point of physiologic tolerance. He declares that the duration of flutter has apparently little effect on the amount of digitalis required.

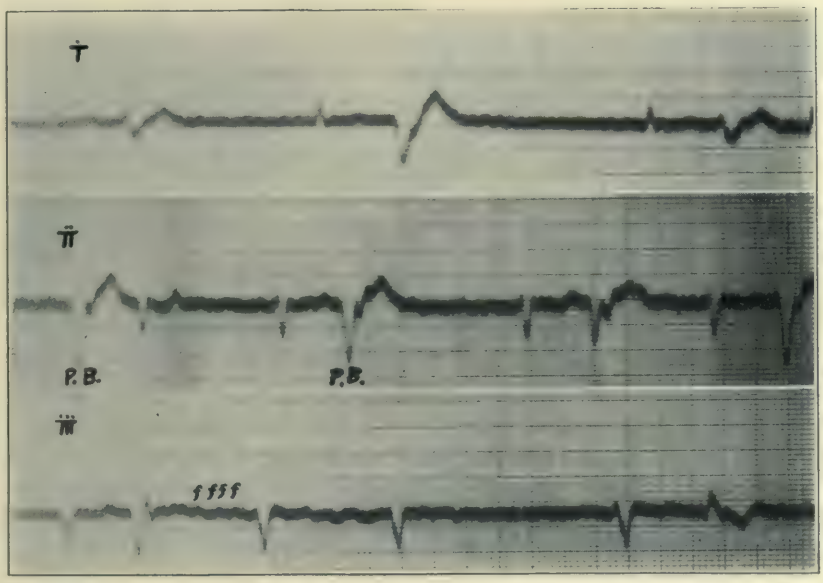

Fig. 17.—(No. 33, Leads I, II, III). Electrocardiogram taken after 940 minims tincture of digitalis had been administered over a period of seventeen days. The auricles are in fibrillation. Digitalis coupling is marked.

Cary Eggleston,[33] after careful tests, says that "the average therapeutic dose of digitalis given orally to man is 0.146 cat unit, or about 0.146 c.c. of an average high grade tincture per pound of body weight." In about half of his cases full therapeutic effects were secured with doses within 15 per cent. above or below this average. Furthermore, he says that "age, sex, and cardiac condition do not seem to influence the size of dose required." Taking this dosage as a standard, we gave

32. Tallman, M. H.: Auricular Flutter; Report of Cases, Northwest. Med., 1916, **15,** 145; abstr. in Jour. Am. Med. Assn., 1916, **66,** 1832.

33. Eggleston, Cary: Digitalis Dosage, The Archives Int. Med., 1915, **16,** 1.

our patient, who weighed something under 180 pounds, about 2½ times the average dose (180 × 0.146 c.c. = 26.28 c.c. = "average dose" our patient; actual amount given = 62.6 c.c.). Eggleston says he obtained earliest therapeutic effects with large individual doses in thirteen hours, which is in conformity with the increase in block noted by us after 100 minims of the tincture had been taken in less than thirty hours.

The effect of digitalis on the T wave was interesting. During flutter, Lead I was the only lead in which the T wave was not obscured by the P waves, so we shall consider only the T of that lead. It is definitely upright and of an amplitude within normal limits on all plates taken up to the beginning of digitalis administration. After 200 minims of digitalis had been given, the T wave decreased in height. This effect, however, was not constant, since several plates taken during digitalis administration showed an amplitude equal to that noted before this drug was begun. After discontinuance of digitalis, the T wave was intermittently low during a period of eighteen days, after which period low waves did not reappear.

It is difficult to decide when the change in mechanism from flutter to fibrillation has been due to digitalis, since such change has occurred spontaneously. It is also difficult to know when the drug should be discontinued. Under ordinary circumstances, digitalis is stopped only with the onset of fibrillation. However, in our case marked toxic effect — coupling — was noted while the auricles still remained in flutter and after the administration of only 200 minims of the tincture. In view of the fact that our object — fibrillation — had not been attained, it was decided to disregard the warning, and our decision was subsequently justified by the fact that under continued use of the tincture no further toxic manifestations appeared, while the desired change in mechanism took place after the further administration of 740 minims of the drug. Digitalis was now discontinued, as observation has shown that a return to normal mechanism may be prevented by a further use of the drug after this stage in treatment. This return cannot be promised, for in but twenty-two of Ritchie's fifty-three cases was there a return to the normal mechanism. Such return has occurred as early as the third, and as late as the twenty-third day after digitalis has been stopped. It has now (at time of writing) been more than four months since we discontinued the first course of digitalis in our case, and four weeks since discontinuance of a second course. Fibrillation was still present when the patient was last observed, March 30. His apex rate was about 75, without pulse deficit. He returned to his work, using some caution in the amount of daily effort, and was without symptoms or physical signs of decompensation. If we can keep him in this state, with the possibility of return to normal, improbable though it be, we believe his condition to be better than when in flutter with the increased

rate on slightest exertion. In the chapter on treatment, Ritchie[5] says: "We know that once auricular fibrillation is induced, there is a distinct tendency for it to persist. This is a most undesirable event." That it may not be wholly undesirable is shown by the result in our case.

In urgent cases, strophanthin, injected intravenously, has given excellent results. The other elements of treatment — rest, sedatives, treatment of causal factors — are based on the same principles as in other disturbances of cardiac mechanism and need not be considered here.

SUMMARY

A case is presented which shows most of the well known characteristics of auricular flutter.

The contour of the P deflection is discussed. We believe that in our case the P wave is diphasic, primarily downward, but that this is not a constant form in flutter. The origin of auricular impulses is believed to be ectopic.

The usual difficulties were encountered in the measurement of the A_s-V_s interval in flutter. We believe that in our case there was a marked variation of this interval. No constant variation was observed in relation to the varying degrees of block, although there was a suggestion of some difference in conduction time as the result of right and left vagus stimulation. The A_s-V_s interval was prolonged by digitalis in flutter as in normal mechanism.

Emphasis is laid on the variation of auricular rate as found in the individual case of flutter, a fact which has been usually overlooked.

Blood pressure studies showed marked daily variation of the systolic pressure as observed during flutter and fibrillation. There was a marked constancy of the diastolic pressure. Rather definite points were noted during fibrillation, in our case, corresponding to the systolic and diastolic pressures as taken in the usual manner during normal mechanism, an observation which led one of us to question the value of "average systolic" blood pressure readings in fibrillation.

Vagus stimulation by pressure, either over carotid artery or eyeball, produced ventricular slowing or standstill, as has been noted by previous observers. Pressure over the carotids was found to be the more reliable method, while better effects were noted with stimulation of the right vagus than of the left. However, this result was inconstant. In one instance an artificial Stokes-Adams syndrome was produced by vagus pressure. Latent period and residual effect after vagus stimulation were confirmed, as was the absence of effect on the auricle. Except for action on ventricular rate, no difference was noted between effects of right and left vagus pressure. Vagus stimulation produced like results in fibrillation and in flutter.

The prolongation of the refractory stage of heart muscle under the influence of repeated stimuli is noted as a possible explanation of the auriculo-ventricular dissociation in flutter and fibrillation.

Our case again emphasizes the necessity for the use of graphic methods in the diagnosis of flutter and of the transition to fibrillation.

Finally, the effect of digitalis during treatment—its very early effect on conduction, its possible effect on auricular rate, the change in the T wave, and the large amount necessary to change the mechanism to fibrillation — is considered at some length.

St. Francis Hospital.

CLINICAL STUDIES ON THE RESPIRATION

III. A MECHANICAL FACTOR IN THE PRODUCTION OF DYSPNEA IN PATIENTS WITH CARDIAC DISEASE *

FRANCIS W. PEABODY, M.D.
BOSTON

In a former paper[1] observations were reported on the effect of increasing the carbon dioxid content of the inspired air in normal persons and in patients with cardiac disease. It was shown that in normal persons the minute-volume of air breathed doubled when the concentration of carbon dioxid was between 4.2 and 5.4 per cent., and that cardiac patients, excepting those with a demonstrable acidosis, behaved in an approximately similar manner. In order to obtain further information as to the mechanism of dyspnea in heart disease additional observations have been made in which the subjects have been allowed to continue breathing until the carbon dioxid in the inspired air produced a high degree of dyspnea. It was hoped that at the height of dyspnea more difference would be found between the mechanism of the respiration in the normals and in the cardiac patients than was obvious when lower concentrations of carbon dioxid were being breathed. Such, indeed, has proved to be the case, and the demonstration of one of the abnormalities of the respiration in dyspneic cardiac patients forms the basis of the present communication.

METHOD

The method used has been described in detail in the paper referred to. Briefly it consists in having the subject breathe through valves which separate the expired from the inspired air. The expired air passes through a closed circuit and is then rebreathed, so that the inspired air contains a progressively rising percentage of carbon dioxid and a falling percentage of oxygen. Samples of the inspired air are then taken every two minutes and analyzed for carbon dioxid. A calibrated volumetric recording spirometer is connected with the closed circuit and the volume of each respiration is registered on the drum of a kymograph. With the aid of an electric timer, the minute-volume

* Submitted for publication April 30, 1917.

* From the Medical Clinic of the Peter Bent Brigham Hospital and the Medical School of Harvard University.

1. Peabody: Clinical Studies on the Respiration. No. 1. The Effect of Carbon Dioxide in the Inspired Air on Patients with Cardiac Disease, THE ARCHIVES INT. MED., 1915, **16,** 846.

of air breathed can be thus easily determined. It will be noticed that in all instances the minute-volume at the beginning is unusually high. This is due in part to the fact that only a short time was given for the subject to accustom himself to mouth breathing, and in part it depends on the fact that the figures given are the actual measurements uncorrected for either temperature or barometric pressure. The subjects were either comfortably seated in a chair, or they were in bed, propped up with cushions in an erect position. The experiment was continued until the subject was so intensely dyspneic that he was unable to continue any longer. On breathing atmospheric air again dyspnea disappeared almost immediately and respiration became normal. In a few instances a troublesome headache persisted. As was to be expected, it was possible to continue the experiment longer, and thus produce a relatively higher degree of dyspnea in normal persons than in cardiac patients, since several of the latter were seriously sick. Only those have been selected for the present discussion, however, who showed a willingness and an interest in cooperation, and who persisted in continuing until they became extremely breathless.

NORMAL SUBJECTS

The four normal subjects were young men between the ages of 25 and 33 years. Only one (F. G. B.) had done much athletic work and he had not been in strict training for several years. Their response to

TABLE 1.—DATA AT BEGINNING AND END OF OBSERVATION OF FOUR NORMAL SUBJECTS

Subject	Rate of Respiration		Single Respiration, C.c.		Minute-Volume, Liters		Per Cent. of Increase in Minute-Volume at End	Per Cent. of CO_2 in Inspired Air at End
	Initial	Final	Initial	Final	Initial	Final		
D. W. C.	18	32	542	2,328	9.8	74.5	761	7.35
F. G. B.	16	25	592	2,980	9.5	74.4	786	9.08
F. W. P.	12	29	734	2,814	8.6	81.6	947	7.11
J. C. W.	17	30	627	2,260	10.7	67.7	635	9.22

the stimulus of the carbon dioxid was within normal limits, the initial ventilation being doubled by a concentration of carbon dioxid agreeing closely with that found for normal subjects in the previous paper. In Table 1 are the essential data at the beginning and at the end of the observation.

Reference to Table 1 as well as to the graphic records of the respiration (Figs. 1 and 2) during the experiments show that under the

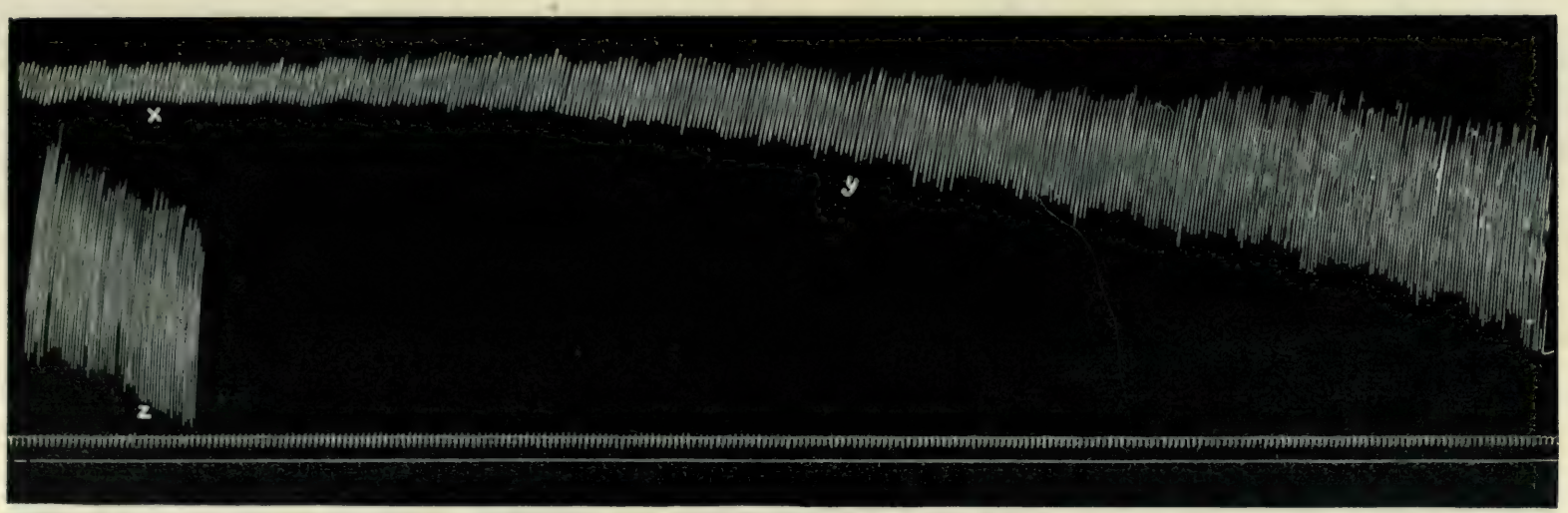

Fig. 1.—F. G. B.; normal. Sept. 30, 1915. At X (beginning) inspired air contained 0.45 per cent. carbon dioxid; minute-volume = 9.5 liters. At Y (after twelve minutes) inspired air contained 5.04 per cent. carbon dioxid; minute-volume = 18.4 liters. At Z (after twenty-four minutes) inspired air contained 9.08 per cent. carbon dioxid; minute-volume = 74.4 liters. Figures 1 to 6 are graphic records of the respiration of normal subjects and of patients with heart disease while breathing air containing progressively increasing amounts of carbon dioxid. Inspiration is represented by a down stroke and expiration by an up stroke. The length of each stroke corresponds quantitatively to the volume of the respiration. The timer marks five-second intervals. All tracings are to be read from left to right.

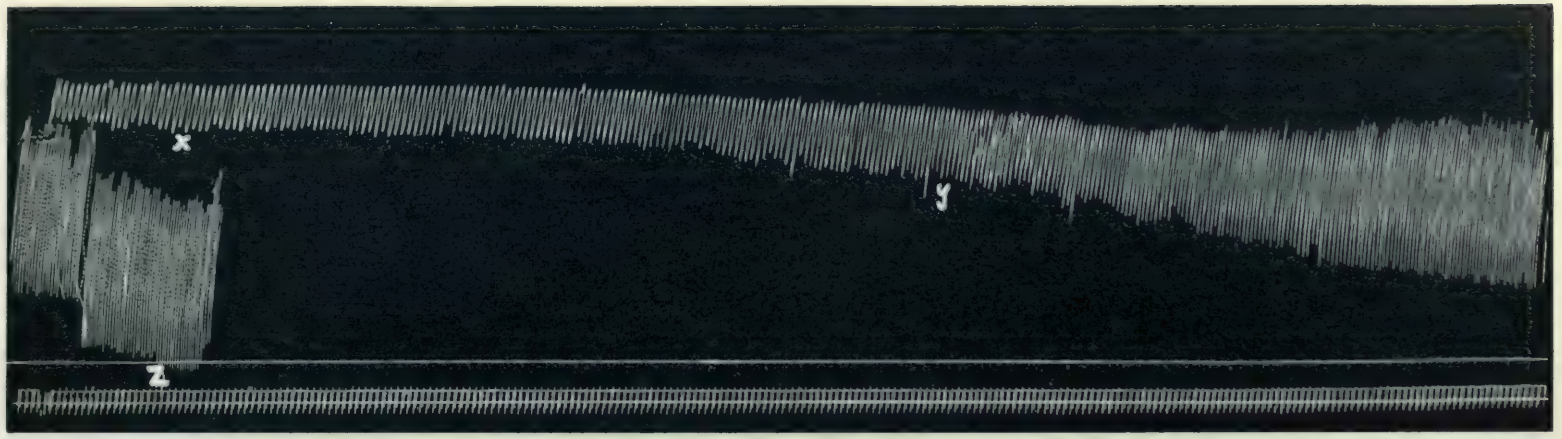

Fig. 2.—F. W. P.; normal. June 10, 1915. At X (beginning) inspired air contained 0.21 per cent. carbon dioxid; minute-volume = 8.6 liters. At Y (after twelve minutes) inspired air contained 4 per cent. carbon dioxid; minute-volume = 17.8 liters. At Z (after twenty-two minutes) inspired air contained 7.11 per cent. carbon dioxid; minute-volume = 81.6 liters.

influence of the rising percentage of carbon dioxid in the inspired air the minute-volume of air breathed increases, and that the increase in minute-volume is brought about by a rise in both the rate and depth of respiration. The average rate at the beginning was 16, and at the end it was 29 per minute. The average volume per single respiration was 624 c.c. at the beginning and 2,595 c.c. at the end. The average rate of respiration was thus nearly doubled, and the average depth was approximately quadrupled. The average increase in minute-volume, however, was nearly eight times that of the initial figure. The percentage of carbon dioxid in the inspired air at the time when the subjects were forced to stop on account of dyspnea varied from 7.11 to 9.22. The relation between the carbon dioxid in the inspired air and the percentage increase in minute-volume is not as definite with these high concentrations as it was found to be with the lower concentrations of carbon dioxid. J. C. W., who was breathing the highest percentage of carbon dioxid at the end of the observation, had the least increase

TABLE 2.—Data at Beginning and End of Observation of Five Patients with Cardiac Disease

Subject	Rate of Respiration		Single Respiration, C.c.		Minute-Volume, Liters		Per Cent. of Increase in Minute-Volume at End	Per Cent. of CO_2 in Inspired Air at End
	Initial	Final	Initial	Final	Initial	Final		
W. H. A.	15	20	589	1,164	8.8	23.3	264	4.27
W. E. M.	15	39	450	600	6.5	23.4	360	4.60
J. W. O'M.	15	38	...	.....	10.2	25.9	254	4.97
J. S.	28	36	450	800	10.4	28.0	270	5.62
J. S.	25	26	475	900	11.7	23.4	201	4.97
W. E. W.	31	35	450	1,093	14.0	28.3	274	4.95

in minute-volume. This is especially noteworthy since much greater subjective symptoms were experienced by him than by the other subjects both during and after the observation. He was extremely dyspneic and was also troubled by dizziness, tingling of the hands and by a severe headache which began early in the course of the experiment and persisted for some hours after it was ended. Cyanosis was not marked. These symptoms were apparently due to carbon dioxid poisoning, and it seems probable that had he been able to keep his pulmonary ventilation higher he would have had less accumulation of carbon dioxid in the blood and tissues, and would have gone through the experiment with as little distress as did the other subjects who were able to regulate their respiration so that no excessive retention of carbon dioxid took place.

CARDIAC PATIENTS

There are six observations on five patients with cardiac disease which are suitable for the present study. All of them were severely afflicted subjects, in whom dyspnea was produced either by slight or by very moderate exertion.

Table 2 shows the data at the beginning and at the end of the various observations. J. W. O'M., J. S. and W. E. W. responded quite normally to the carbon dioxid, their minute-volumes being doubled by concentrations of carbon dioxid which would produce the same effect in normal persons. The other two subjects were more sensitive to the action of carbon dioxid. In the case of W. H. A., whose minute-volume became doubled while he was breathing air containing 3.64 per

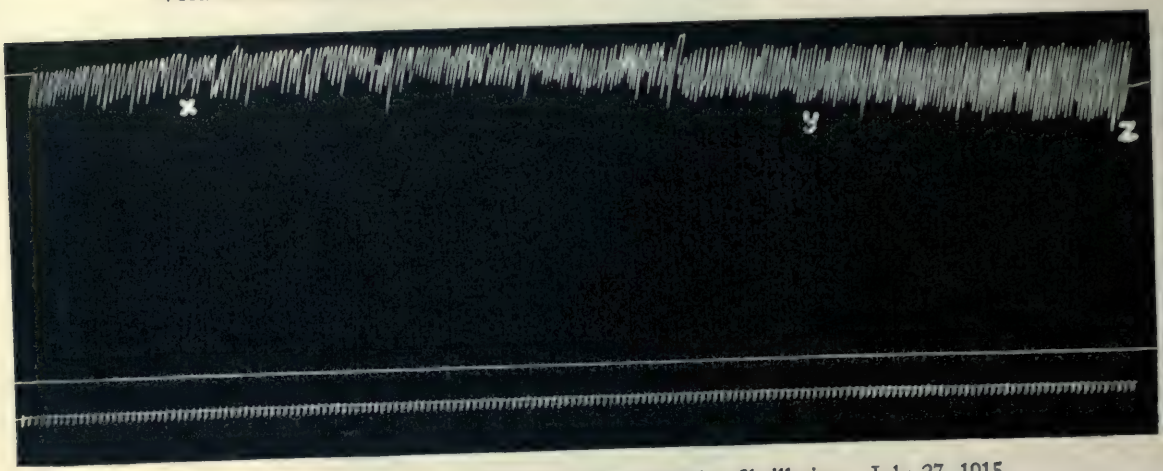

Fig. 3.—W. H. A.; chronic myocarditis, auricular fibrillation. July 27, 1915. At X (beginning) inspired air contained 0.39 per cent. carbon dioxid; minute-volume = 8.8 liters. At Y (after ten minutes) inspired air contained 2.88 per cent. carbon dioxid; minute-volume = 14.7 liters. At Z (after fourteen minutes) inspired air contained 4.27 per cent. carbon dioxid; minute-volume = 23.3 liters.

cent. carbon dioxid, this is accounted for by the presence of a slight acidosis. The alveolar carbon dioxid was 36.3 mm. (Plesch method). W. E. M. doubled his ventilation when breathing between 2.3 and 3.0 per cent. carbon dioxid, but the cause of this increased sensitiveness is not apparent as there was no evidence of acidosis. He was, however, in poor condition and had been a long time decompensated.

A comparison of the respiration at the beginning of the experiment and at the height of the dyspnea shows several points of interest. The average rate of respiration was 21 per minute at the beginning (excluding W. E. W., in whose case it was 19) and 33 per minute at the end. The average volume per single respiration was 482 c.c. at the beginning and 911 c.c. at the end. Thus when the observation had

to be stopped on account of dyspnea the average rise of respiration rate was nearly as great as with the normal subjects, but the depth of respiration had only been doubled, while with the normal subjects it was fourfold the initial value at the end of the experiment. The result of not increasing the depth of respiration to a greater degree is still more strikingly shown when one considers the rise of the minute-

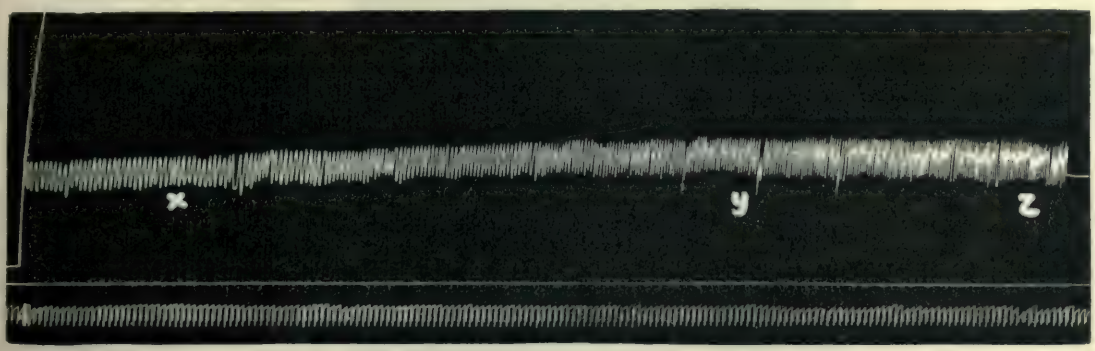

Fig. 4.—W. E. M.; mitral stenosis, auricular fibrillation. Dec. 26, 1914. At X (beginning) inspired air contained 0.18 per cent. carbon dioxid; minute-volume = 6.5 liters. At Y (after ten minutes) inspired air contained 3.07 per cent. carbon dioxid; minute-volume = 15.1 liters. At Z (after fourteen minutes) inspired air contained 4.60 per cent. carbon dioxid; minute-volume = 23.4 liters.

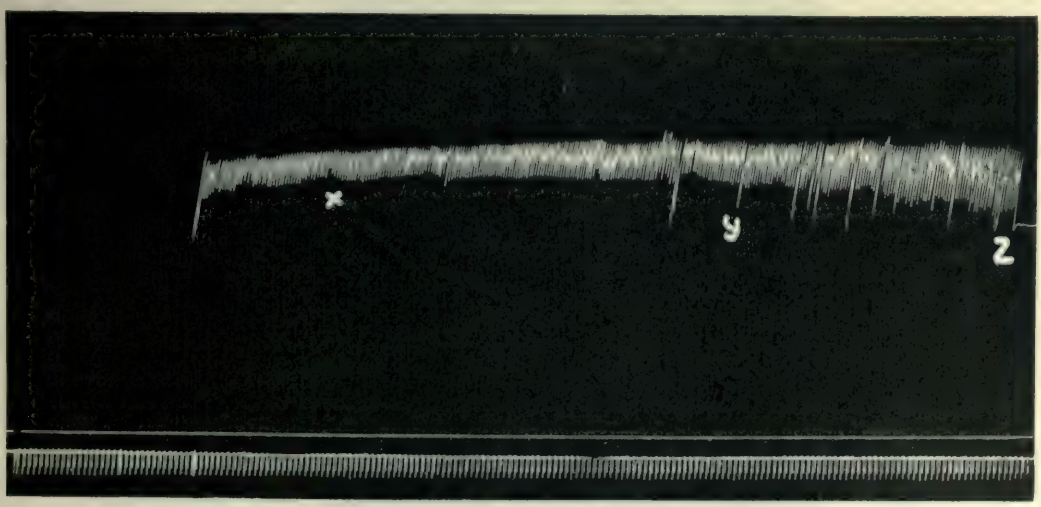

Fig. 5.—J. S.; mitral stenosis and insufficiency. Dec. 22, 1914. At X (beginning) inspired air contained 0.43 per cent. carbon dioxid; minute-volume = 11.7 liters. At Y (after eight minutes) inspired air contained 3.16 per cent. carbon dioxid; minute-volume = 18.1 liters. At Z (after twelve minutes) inspired air contained 4.97 per cent. carbon dioxid; minute-volume = 23.4 liters.

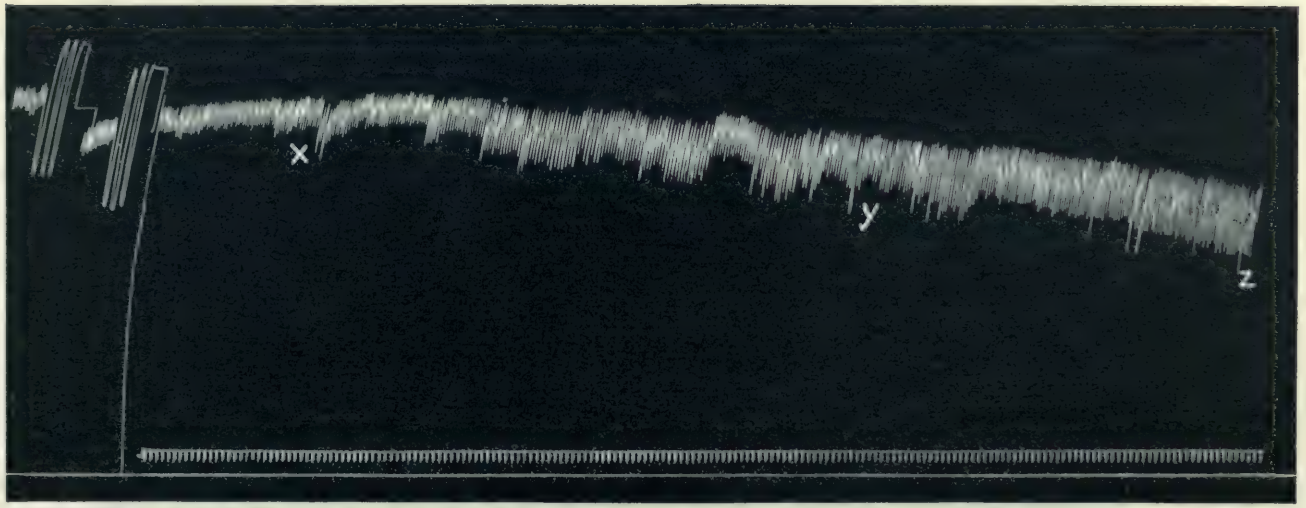

Fig. 6.—W. E. W.; mitral stenosis. Oct. 7, 1917. At X (beginning) inspired air contained 0.50 per cent. carbon dioxid; minute-volume = 14 liters. At Y (after ten minutes) inspired air contained 3.28 per cent. carbon dioxid; minute-volume = 20.2 liters. At Z (after fifteen minutes) inspired air contained 4.95 per cent. carbon dioxid; minute-volume = 38.3 liters.

volume. The average increase in minute-volume was approximately 800 per cent. with the normal subjects, but with the cardiac patients it was only 270 per cent. A comparison of the graphic records of the respiration (Figs. 3, 4, 5 and 6) made during the two sets of observations shows more clearly than do figures the differences in the respiration of the normal subjects and of the cardiac patients. From them it is quite evident that when the cardiac patients had to stop the experiment on account of dyspnea, they had increased the rate of respiration much as do the normal subjects, but the depth of respiration was increased to a much less degree. The percentage of carbon dioxid in the inspired air at the height of the dyspnea varied from 4.27 to 5.62. The cardiac patients thus became dyspneic when they were breathing a much lower percentage of carbon dioxid than was the case with the normal persons.

DISCUSSION

As the result of any stimulus to the respiratory center, whether, for instance, it is the carbon dioxid produced by the increased metabolism of exercise or whether it is a high percentage of carbon dioxid in the inspired air, the pulmonary ventilation becomes increased. There is, indeed, apparently a fairly close relation between the amount of the increase in ventilation as measured by the minute-volume of air breathed and the amount of the stimulus. As long as one can meet the demand for an increased ventilation easily and without undue exertion there is merely hyperpnea, but no dyspnea. The increased carbon dioxid is excreted normally and there is no accumulation in the blood and tissues. When, however, the stimulus to respiration is such as to require a greater ventilation of the lungs than the person can for any reason meet without undue exertion the subjective symptoms of dyspnea begin to develop. Thus anything that interferes with the normal ability to increase the minute-volume of air breathed tends to make the subject unduly sensitive to the development of dyspnea.

In the experiments just described, it was seen that under the influence of progressively rising amounts of carbon dioxid in the inspired air the rate and depth of the respiration of normal persons increased, until the minute-volume reached an average of approximately eight times its normal value. When the minute-volume had risen to this point the subjects were breathing as rapidly and as deeply as possible, and it was necessary to stop the experiment on account of extreme dyspnea. Patients with cardiac disease responded in nearly the same manner to the lower concentrations of carbon dioxid. A given amount of carbon dioxid produced about the same increase in pulmonary ventilation in the cardiac patients as it did in the normal subjects. They suffered from dyspnea, however, much more rapidly

than did the normal subjects and could not breathe such high concentrations of carbon dioxid, because they were unable to increase the minute-volume of air breathed to the same extent. In the cases studied dyspnea was experienced even when the minute-volume was only about two or three times its normal value. This inability to increase the pulmonary ventilation any higher is shown to depend on the fact that cardiac patients cannot increase the depth of their respiration as well as normal persons.

The essential difference between normal subjects and patients with heart disease with regard to the production of dyspnea is thus not that cardiac patients are necessarily more sensitive to any given stimulus to the respiratory center, but that they cannot stand as great a stimulus. Cardiac patients become dyspneic easier than normal subjects because they were unable to meet the rising stimulus to respiration with an adequate increase of pulmonary ventilation. The limitation of the depth of breathing is thus an important factor in the production of dyspnea in patients with heart disease. Rubow[2] has already made incidental references to this point in his article on "Die Kardiale Dyspnoe."

It has long been known[3] that in many patients with heart disease the vital capacity of the lungs, that is, the volume of the greatest possible expiration after the deepest inspiration, is decreased below the normal. The demonstration in the observations reported here of the significance of the ability to breathe deeply in relation to the production of dyspnea has led to a detailed study on the subject of the vital capacity in patients with cardiac disease and its relation to dyspnea. The results of this investigation will be published separately.

2. Rubow: Ergebn. d. inn. Med. u. Kinderh., 1909, **3**, 92.
3. Arnold: Ueber die Athmungsgrösse des Menschen, Heidelberg, 1855, p. 139.

CLINICAL STUDIES OF THE RESPIRATION

IV. THE VITAL CAPACITY OF THE LUNGS AND ITS RELATION TO DYSPNEA*

FRANCIS W. PEABODY, M.D., AND JOHN A. WENTWORTH, M.D.
BOSTON

INTRODUCTION

In an earlier paper[1] in this series, observations were described on the production of dyspnea in normal subjects and in patients with cardiac disease by means of increasing amounts of carbon dioxid in the inspired air. It was found that patients with heart disease became dyspneic more easily than did healthy subjects, and this tendency seemed to depend largely on their inability to increase the depth of respiration in a normal manner. A few preliminary determinations showed that this inability to breathe deeply corresponded to a diminished vital capacity of the lungs as measured by the volume of the greatest possible expiration after the deepest inspiration. Since any condition which limits the possibility of increasing the minute-volume of air breathed must be an important factor in the production of dyspnea, it appeared worth while to undertake an extensive study of the vital capacity of the lungs in those diseases in which dyspnea is a frequent symptom. The present paper deals with observations on the vital capacity in a large series of normal persons, of patients with heart disease and of patients with various other clinical conditions. Particular attention has been paid to the findings in cardiac disease because they appear to be of some practical significance. The results reported indicate that there is a very close parallelism between a decrease in the vital capacity of the lungs and the tendency to dyspnea.

HISTORICAL

No attempt will be made to give here a complete review of the literature which relates to the vital capacity of the lungs, but attention may be called to a few important contributions on the subject. In 1846 Hutchinson[2] reported a study of the relation of the vital capacity to the height in a large series of normal persons. In 1855 Arnold[3] published an extensive and carefully compiled monograph on the vital

* Submitted for publication April 30, 1917.

* From the Medical Clinic of the Peter Bent Brigham Hospital and the Medical School of Harvard University.

1. Peabody, F. W.: See page 433, this issue.
2. Hutchinson, Jonathan: Med. Chir. Tr., London, 1846, **29.**
3. Arnold: Ueber die Athmungsgrösse des Menschen, Heidelberg, 1855.

capacity in health and disease. He studied the influence of age, sex, height, size and expansion of chest, and habit of life on the vital capacity, and showed that all of these factors may have considerable effect on it. The changes in the vital capacity in a number of pathologic conditions including heart disease are also described by him. Bohr[4] in 1907 published his important investigation on the "Mittellage" of the lungs, including determinations of the residual, reserve and complemental air, the total lung volume and the vital capacity. The effects produced on them by changes of position, by exercise, by the inspiration of gases, as well as the variations met with in different persons are discussed in detail. Rubow[5] measured the vital capacity in a number of patients in connection with his studies on the respiration in heart disease, but his chief interest was the change in the "Mittellage" of the lungs. Bittorf and Forschbach[6] studied the lung volumes in pathologic conditions such as emphysema, heart disease and pleural effusions, and report with other data, the change in the vital capacity. Siebeck[7] has made similar determinations of the lung volumes, and finds in accord with other investigators a low vital capacity of the lungs in heart disease.

METHOD

The vital capacity of the lungs is the volume of air which can be expired after the deepest possible inspiration. It was determined in these observations by means of a calibrated recording spirometer designed by Krogh.[8] The movements of the spirometer with inspiration and expiration are written on the smoked drum of a slowly moving kymograph, and permanent records are obtained from which the volume of the respiration can be measured by the use of a graduated scale, with an accuracy of approximately 10 c.c. (Fig. 1). The subjects sit upright in bed or on a chair, and breathe in and out as deeply as possible through a rubber mouthpiece, the nose being closed by a tight clip. The spirometer was placed on a movable carriage, so that it could be taken to the bedside of patients whom it was not desired to bring to the laboratory (Figs. 2 and 3). No corrections were made for temperature, pressure, or water vapor tension.

No particular difficulty was experienced in obtaining satisfactory determinations of the vital capacity. Care was always taken to explain to the patients the desired object, and it was necessary to urge them to breathe as deeply as possible. Strict attention must be paid to this point, for otherwise the volume of the respiration is too low, and does

4. Bohr: Deutsch. Arch. f. klin. Med., 1907, **88,** 385.
5. Rubow: Deutsch. Arch. f. klin. Med., 1908, **92,** 255.
6. Bittorf and Forschbach: Ztschr. f. klin. Med., 1910, **70,** 474.
7. Siebeck: Deutsch. Arch. f. klin. Med., 1910, **100,** 204.
8. Krogh: Skandin. Arch. f. Physiol., 1912, **27,** 100.

not represent the true vital capacity. As would be expected, the first attempt was often unsatisfactory, but the second or third attempt, after the subject had become accustomed to the apparatus, and after he appreciated what was required of him, almost invariably gave reliable results. The observations were made rapidly, and usually consumed only from three to five minutes for each person. In a small number of patients satisfactory results could not be obtained. This was either because it was impossible to make them understand what they were

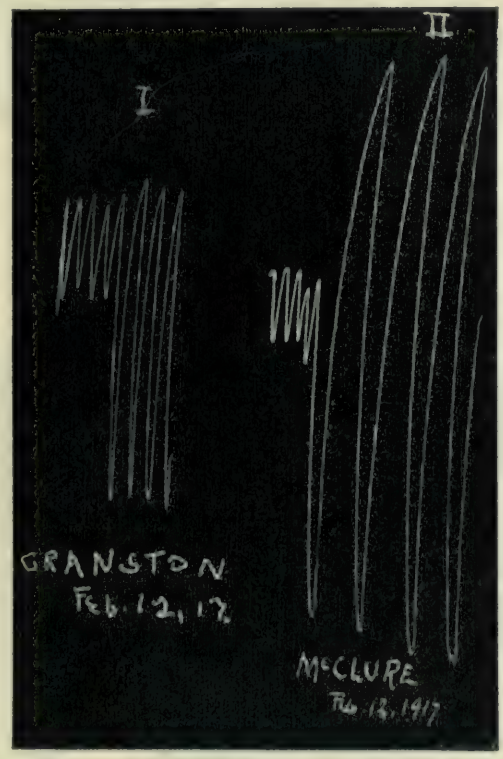

Fig. 1.—Records of vital capacity of the lungs: I, Patient with severe heart disease beginning to regain compensation; vital capacity was 2,500 c.c. or 52 per cent. of normal standard. II, Normal individual of about the same size; vital capacity was 4,620 c.c. or 96 per cent. of normal standard.

supposed to do, or because they were unwilling to cooperate. In such instances, it was, of course, necessary to discard the records. A little experience enables one to judge accurately as to whether or not the subject is actually breathing as deeply as possible.

Variations in the vital capacity as determined when sitting erect in bed or on a chair were small. Frequent observations have shown that the changes in vital capacity from day to day in normal persons, and

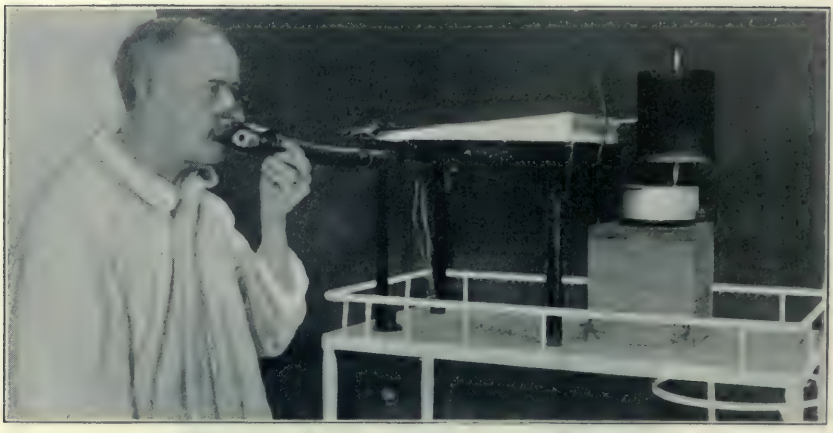

Fig. 2.—Recording spirometer, showing three-way valve and nose-clip.

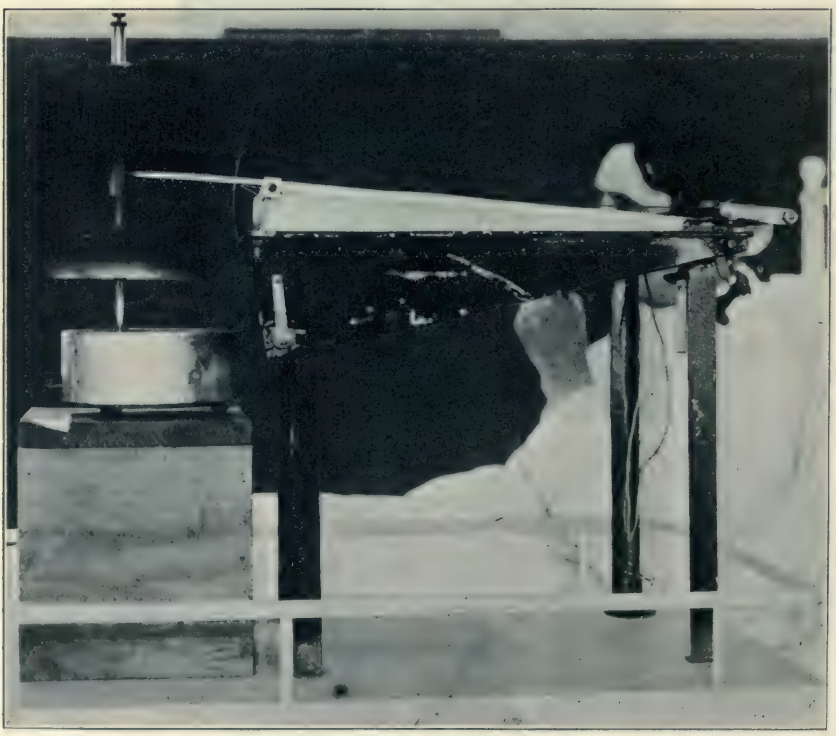

Fig. 3.—Recording spirometer, showing registering of respiration on drum of kymograph.

in patients whose clinical condition remains constant are practically negligible. The effect of posture was studied in two men. The vital capacity was first measured with the subject standing straight, and then again after he had assumed an exaggerated "slumping," round-shouldered posture in which the thorax acted at a great disadvantage. Such an extreme position is rarely met with, but the maximum difference in the vital capacity under the two conditions was only 590 c.c., or 12 per cent.

In order to simplify the technic of determining the vital capacity we have recently made use of a small portable spirometer of the ordi-

Fig. 4.—Portable spirometer, showing calibrated wheel at the top. This spirometer is made of copper and the bell is of aluminum.

nary type which holds 8 liters of air (Fig. 4). With this apparatus it is not possible to obtain graphic records, but the depth of respiration is measured directly on the calibrated wheel. The chief difference between this spirometer and the recording spirometer is that in the latter the subject breathes in and out several times, and since the lungs and spirometer form a closed system there is no chance for leakage, while with the former the subject takes a deep inspiration and blows it out into the spirometer. With an untrained person it would seem

possible that some air might be lost before the tube to the spirometer was inserted in the mouth. The two methods have been compared, however, by observations on a series of fifty normal persons and patients, and a strikingly good correspondence between them has been found. The greatest variation in the vital capacity by the two methods was 8 per cent., and in thirty-nine of the fifty persons studied the results agree within 5 per cent. The higher volumes were usually, but not always, obtained with the recording spirometer. It would thus seem that in the clinical study of the vital capacity of the lungs, where the highest degree of accuracy is not to be expected, a well balanced spirometer of the ordinary type may be used satisfactorily.

A. VITAL CAPACITY OF NORMAL ADULTS

In order to have normal standards of the vital capacity with which to compare the results obtained in disease, a study has been made of 140 healthy persons including physicians, nurses, medical students and a number of ward patients who would be classed as normal from the present point of view. The history of each person was investigated, especially with regard to any tendency to dyspnea, and in many instances a physical examination was made. The subjects ranged between 20 and 50 years of age, but the majority were between 20 and 30 years. They were on the whole a representative group of normal people in every day life. A limited number of observations was made on children, but not enough to give any reliable normal standards. It has, therefore, seemed best not to include any data on the vital capacity of children, either in health or in disease, in the present paper. Since it is generally known that the vital capacity decreases with advancing years, and since a number of the patients studied were over 50 years of age, it would have been better if it had been possible to study more elderly normal persons. Such subjects were, unfortunately, not easy to obtain; but in spite of this the normal standards established appear to be of practical value.

The vital capacity varies normally, as shown by Arnold, with many conditions. Age, sex, height, weight, the size and flexibility of the thorax and physical training may each and all influence it. It was felt to be important, however, in the present clinical study to have as simple a method of standardizing results as possible and, after attempting various ways, it was found that a classification based on sex and height was practical and sufficiently accurate.

In the determination of the normal standards of vital capacity, therefore, the observations on 140 normal persons have been grouped according to sex and for each sex three subgroups have been made on the basis of height. The average normal vital capacity has been determined for each subgroup. Having thus established the normal standards, it has been our custom to refer all subsequent determina-

tions to these and to express them in percentage of the appropriate normal.

Ninety-six normal males were studied and divided into three groups according to their height. Group I includes those who were 182.5 cm. (6 feet) tall or over, and the normal standard computed was 5,100 c.c. Group II consisted of men between 173.5 cm. (5 feet, 8½ inches) and 182.5 cm. (6 feet) tall, and the average vital capacity, which was 4,800 c.c., was taken as the normal. Group III was comprised of persons whose height was between 173.5 cm. (5 feet, 8½ inches) and 159.5 cm. (5 feet, 3 inches). The normal standard of this group was 4,000 c.c. With one exception the vital capacity in all the males examined varied between 86 and 121 per cent. of the normal figure, while 84 per cent. were within 10 per cent. of the normal. The largest vital capacity was 7,180 c.c., or 141 per cent. This was found in a powerful man (G. E. H.) who had recently been a member of the varsity crew, track and football teams in a large university. Four other members of this group had a vital capacity of 6,000 c.c. or over, and all had undergone severe athletic training. Table 1 gives the details of the determinations of vital capacity in the normal males and shows the actual and percentage variations from the standard adopted in each group. It will be noted that in Group I only 63 per cent. of the subjects had a vital capacity within 10 per cent. of the normal. This is explained in part by the small number of observations made in this group, but more particularly by the fact that many of these large men were highly trained athletes in whom one would expect to find the vital capacity unusually high. There was a difference of 2,150 c.c. between the highest and the lowest values obtained for the vital capacity in Group I, but if G. E. H., who is 190 cm. (6 feet, 3 inches) tall, be excluded, the difference is only 1,170 c.c. In Group II there was a difference of 1,500 c.c., and in Group III the difference between the highest and the lowest members is 1,630 c.c. There may thus be quite a variation in the actual vital capacity of normal persons of approximately the same height.

TABLE 1.—The Vital Capacity of the Lungs of Normal Males

Group	Number Studied	Height in Feet and Inches	Normal Vital Capacity, C.c.	Number Within 10 per Cent. of Normal	Highest Vital Capacity	Lowest Vital Capacity	Highest per Cent.	Lowest per Cent.	Number Below 90 per Cent. of Normal
I	14	6′ +	5,100	9	7,180	5,030	141	99	0
II	44	Over 5′8½″ to 6′	4,800	41	5,800	4,300	121	90	0
III	38	5′3″ to 5′8½″	4,000	31	5,080	3,450	127	86	1

Special attention is called to the last column in Table 1. It will be seen from this that only one of the ninety-six normal subjects had a vital capacity which was more than 10 per cent. below the appropriate normal standard. This is of particular importance from the standpoint of the present paper, since all of the pathologic conditions which affect the vital capacity produce a decrease of it. For practical purposes, then, the significant fact is the demonstration that healthy males almost invariably have a vital capacity of 90 per cent. or more of the normal standard. A decrease in the vital capacity below 90 per cent. will therefore suggest some pathologic condition.

The most important factor inducing extreme variation in the vital capacity of normal subjects of similar size appears to be athletic training. The average vital capacity of ten highly trained athletes was 120 per cent. of the normal standards. Table 2 shows the actual vital capacity, the percentage of the vital capacity in terms of the normal and a short note as to their athletic experience. The increase of vital capacity had persisted in some of them for several years after strenuous exercise had been last indulged in.

TABLE 2.—The Vital Capacity of the Lungs of Ten Athletes

Subject	Height in Feet and Inches	Vital Capacity, C.c.	Vital Capacity, per Cent. of Normal	Training
G. E. H.	6′ 3½″	7,180	141	Track team, football and crew, 4 years
P. W.	6′ 2¼″	6,100	120	Cross country runner, 4 years
P. N. N.	6′ 2″	6,100	120	Basket ball and track team, 4 years
H. M. R.	6′ 1⅛″	6,000	118	Crew, much general athletics
A. M. G.	6′ 1¼″	6,200	122	Hockey team, football team, crew
H. J.	5′11½″	5,800	121	Cross country runner
F. M. C.	5′11″	5,410	113	Football and track teams
N. R.	5′11½″	5,530	115	Football and track teams
F. C. H.	5′10½″	5,530	115	Cross country runner, 4 years
C. R. M.	5′ 6″	4,690	118	Football team, 3 years; track team 4 years

The women were also subdivided into three groups according to their height. Group I was composed of those who measured over 167 cm. (5 feet, 6 inches) tall, and the average vital capacity was 3,275 c.c. Group II consisted of those who were from 162 cm. (5 feet, 4 inches) up to and including 167 cm. (5 feet, 6 inches). The normal standard for this group was found to be 3,050 c.c. Group III was made up of persons from 154.5 cm. (5 feet, 1 inch) up to and including those who were 162 cm. (5 feet, 4 inches) tall. The standard vital

capacity for this group was 2,825 c.c. Table 3 gives an analysis of variations from the normal standards in the different groups. Unfortunately, the number of female subjects studied is less than one half the number of males, and this may in part account for the greater percentage of variation from the normal. With a single exception the vital capacities were found to be between 86 and 124 per cent. of the normal. The highest vital capacity, which was 135 per cent., was found in a young woman who had been a student at a school for physical culture. Of the forty-four subjects, thirty had a vital capacity within 10 per cent. of the normal. As was seen to be the case with the normal males, however, only a very small number of females had a vital capacity below 90 per cent. of the normal standards. The lowest vital capacity was 86 per cent., and in but five instances did the vital capacity fall so low as to be between 86 and 90 per cent. of the normal.

TABLE 3.—The Vital Capacity of the Lungs of Normal Females

Group	Number Studied	Height in Feet and Inches	Normal Vital Capacity, C.c.	Number Within 10 per Cent. of Normal	Highest Vital Capacity	Lowest Vital Capacity	Highest per Cent.	Lowest per Cent.	Number Below 90 per Cent. of Normal
I	10	Over 5′6″	3,275	5	4,075	2,800	124	86	2
II	13	Over 5′4″ to 5′6″	3,050	9	3,425	2,660	112	88	2
III	21	5′4″ or less	2,825	16	3,820	2,500	135	89	1

As far as our figures go, then, one may state fairly definitely that in normal persons the vital capacity is at least 85 per cent., and almost always 90 per cent. or more of the normal standards adopted for each group. In elderly persons a slight decrease from these standards may be expected.

Since it has been proved that the metabolism depends directly on the body surface area, it seemed to be of interest to discover whether some similar relation exists between the vital capacity and the body surface. In a series of nine cases the surface area has been calculated by the linear formula of Du Bois.[9] From this limited number of observations it appears that there is a fairly constant relationship between the two, in persons of average build who have led approximately the same type of life as far as exercise goes. In highly trained subjects the ratio of the vital capacity to the surface area is higher than in less athletic persons. Table 4 shows the details of these observations.

9. Du Bois and Du Bois: The Archives Int. Med., 1916, **17**, 863.

TABLE 4.—The Vital Capacity and Its Relation to Body Surface Area

Subject	Vital Capacity, C.c.	Vital Capacity, per Cent. of Normal	Surface Area, Square Meter	Vital Capacity per Square Meter Surface Area, Liters	Vital Capacity, Surface Area	Exercise
G. P. G.	4,000	100	1.57	2.55	26	Average
D. A. H.	4,410	110	1.65	2.67	27	Average
W. S. B.	4,710	98	1.73	2.72	27	Average
W. S. N.	4,770	99	1.77	2.70	27	Average
F. W. P.	4,800	100	1.83	2.62	26	Average
F. C. H.	5,360	112	1.87	2.87	29	Quarter mile runner
J. A. W.	5,080	106	1.87	2.72	27	Average
L. W. G.	4,500	94	1.88	2.39	24	Average
G. E. H.	7,180	141	2.12	3.39	34	Much athletics

If L. W. G. is excepted, the average vital capacity of the six men who were not athletes corresponded to 2.66 liters per square meter of body surface. Considerably higher values (2.87 and 3.39 liters) were found in the two athletes. Whether the relationship between the surface area and the vital capacity is actually more constant than is the relationship between height and vital capacity, will only be known after a much larger series of cases has been studied. For the determination of surface area the subject must be weighed stripped, so that unless a considerably higher degree of accuracy were to be obtained, it would be of advantage to maintain the simpler method. It is quite possible that the use of the linear formula for surface area would be valuable when dealing with persons who fall at the limits of two of the height groups. It is in these persons that the greatest deviations from the normal are usually found when height and sex alone are taken into consideration.

B. VITAL CAPACITY OF THE LUNGS IN HEART DISEASE

It has long been known that the vital capacity of the lungs is frequently decreased in heart disease. The present study, which is based on 224 observations on 124 patients confirms this fact, and shows in a striking manner that the clinical condition of the patient, and more especially the tendency to dyspnea varies very directly with the degree to which the vital capacity is diminished. Many types of heart disease are included, and for the present consideration no attempt has been made to differentiate them. The analysis of the results obtained from this considerable series of determinations is simplified if the patients are classified according to their vital capacity. In connection with

each group the various features of clinical importance will be discussed, and such deductions drawn as the observations appear to warrant.

Group I consists of cases with a vital capacity of 90 per cent. or more of the normal. There is thus no diminution below the accepted normal standard for the vital capacity. Twenty-five patients fall into this class. Very few of them complained of any symptoms referable to their hearts. Many of them entered the hospital for other diseases, and the cardiac condition was only found in the course of the routine examination. Dyspnea was no more prominent as a symptom in the histories of these patients than it would be found to be in a similar group of normal persons. Twenty-three of the cases in this group were able to work, and the majority without much restriction. Only two patients were prevented from working on account of heart disease. One of these (G. A.) had a low grade subacute endocarditis, but showed no dyspnea. The other (I. C.) was a neurotic person who complained constantly of precordial pain. It was impossible to tell whether or not the pain was actually due to cardiac weakness, but he was not encouraged to work. A third patient with mitral disease and evidences of hyperthyroidism (I. M.) gave a history of slight dyspnea on exertion, but she showed no breathlessness after climbing two flights of stairs rapidly with one of us. None of the patients in this group have died.

It is thus evident that cardiac patients with a vital capacity of 90 per cent. or more of the normal are almost invariably in a good state of compensation. They do not suffer from dyspnea after marked exertion, and if, as rarely happens, they are prevented from leading a normal life, this is usually on account of cardiac pain or some other disturbance.

Group II consists of cases in which the vital capacity falls between 70 and 90 per cent. of the normal. Forty-one patients, of whom twenty-four are males and seventeen are females, are included in this group. A history of dyspnea on moderate exertion was commonly given by these patients, but the majority could work, and the others with two possible exceptions, could lead a satisfactory, though somewhat restricted life. At the time when the observations on the vital capacity were made, twenty-two were working, four were ready to be discharged from the hospital, and eight were either at home or up and about the wards without symptoms of cardiac insufficiency. It will be well to make brief mention of the clinical condition of the seven remaining patients.

1. F. O., a blacksmith weighing 91 kg., had aortic insufficiency with a rapid heart and rapid respiration. He complained of dyspnea. His vital capacity, July 29, was 85 per cent. He was extremely nervous and his respiration became

much slower when he thought he was not observed. History states that he has had dyspnea for four years, but he admits that he has frequently been able to run up four flights of stairs without getting short of breath.

2. V. R. had cardiorenal disease. His vital capacity was 85 per cent. There was a history of dyspnea on exertion before he entered the hospital, but he has shown no tendency to dyspnea since his admission.

3. C. J. H. was an obese man with chronic myocarditis. His vital capacity was 76 per cent. There was history of dyspnea on exertion. There is no dyspnea at present.

4. A. O., a woman, had double mitral disease and auricular fibrillation. Her vital capacity was 74 per cent. There was slight dyspnea on walking about the ward, increased by going up stairs. She has been working as a clerk most of the time for a year since this observation. Her vital capacity is now 73 per cent.

5. I. C. had cardiorenal disease. There is history of dyspnea, but very little evidence of it in the hospital. Her vital capacity was 76 per cent. Six months later she reentered with uremia and marked acidosis and died. It is probable that some of the dyspnea on her first admission can be accounted for by an acidosis.

6 and 7. Two neurotic women, one of them obese, gave a history of dyspnea on exertion but showed little evidence of it when tested by exercising.

In general, then, it may be said that cardiac patients with a vital capacity of between 70 and 90 per cent. of the normal may have well marked heart lesions, but are usually able to lead a satisfactory although somewhat restricted life. About one half of the patients examined were actually at work, and many of the others were perfectly able to do a limited amount of work. One patient in this group showed signs of cardiac insufficiency even while leading a careful life. Only two patients have died, one of uremia and one suddenly, probably of acute cardiac failure or pulmonary embolism. On the other hand the members of this group differ from those with a higher vital capacity (Group I) in that almost all of them gave a history of dyspnea on moderate exertion, and have a distinctly limited cardiac reserve. A number of them have had periods of more or less severe cardiac decompensation in which there has been a further drop in the vital capacity. These cases are, therefore, to be regarded as border line cases in which the activities must be somewhat limited, but in which, under favorable circumstances, there is little evidence of cardiac insufficiency.

Group III consists of patients whose vital capacity is only from 40 to 70 per cent. of the normal. Sixty-seven patients, forty-one males and twenty-six females, fall into this class. The characteristic feature of this group is that all its members were in a much less favorable clinical condition than were those who had a higher vital capacity. Dyspnea on even moderate exertion was always noted in the history, and was, indeed, usually the most prominent symptom complained of. Even within the group there was a fairly definite relation between the vital capacity and the clinical condition. Thus all patients with a vital

capacity of from 40 to 45 per cent. of the normal were in bed. Some of them were slightly dyspneic even when completely at rest, while the others became dyspneic on the least exertion. With a vital capacity of from 45 to 60 per cent. of the normal, patients were rarely dyspneic while in bed, and most of them could walk slowly around the ward without becoming short of breath. A few were living at home and could come to the outdoor department, but they all had to walk slowly and avoided stairs or hills. When the vital capacity was between 60 and 70 per cent. the patients have usually been able to walk fairly comfortably, many could come to the hospital on foot, and could even go upstairs without any special distress. Only five (7 per cent.) of the persons in this group were at work when they were examined, and in all cases the work done was very light. Twenty-two (33 per cent.) were up and about the wards without symptoms, or were coming to the outdoor department, and twenty-four (34 per cent.) were still in bed at the time of examination. Eleven patients (17 per cent.) whose vital capacity has been found at some time to fall into this group have died. Only one patient, however, with a vital capacity of over 40 per cent., has died of uncomplicated heart disease in the hospital. E. M., who at one time had a vital capacity of 46 per cent., died four months later of uremia. A. C., with a vital capacity of 48 per cent. on April 7, 1916, died two months later of suffocation from a large aortic aneurysm. Five patients, all with a vital capacity which was so low that they only just fell into this group, died at home soon after leaving the hospital. Three others died in the hospital after showing a decrease in vital capacity below the limits of this group. Many of the patients who were discharged from the hospital in fairly satisfactory condition, but with a vital capacity of from 40 to 70 per cent., had entered the hospital on account of cardiac decompensation. At the time of admission they usually had a vital capacity which was below 40 per cent., or only slightly above this figure.

Thus cardiac patients with a vital capacity of from 40 to 70 per cent. of the normal are severely handicapped. They practically always suffer from dyspnea even on moderate exertion. Many of them can get about the house or can walk slowly on the street, but there are few whose activities are not very definitely limited, and only a small proportion are able to undertake any form of work. There is a fairly definite relation between the clinical condition of the patient and the vital capacity even within the group, and those with a vital capacity below 45 per cent. are usually forced to remain in bed. Attacks of severe cardiac decompensation occur with considerable frequency in this group of patients, and the mortality among those who have at some time been members of the group is rather high.

Group IV consists of patients with a vital capacity of 40 per cent. of the normal or less. Twenty-three cases, 11 males and 12 females, were studied in this group. They were all patients whose clinical condition was such that they had to remain in bed, and practically all showed evidences of cardiac insufficiency. Many were definitely dyspneic while absolutely quiet, and the others became short of breath on the slightest exertion. Eight patients whose vital capacity was below 30 per cent., had extreme dyspnea and orthopnea. The lowest vital capacity found was 17 per cent. There was a close relation between the clinical condition and the vital capacity, and as these decompensated patients improved there was a corresponding rise in the vital capacity. Thus G. G., a cardiorenal patient, entered the hospital with a marked orthopnea and a vital capacity of 30 per cent. He improved rapidly, and seven weeks later was at work. At this time his vital capacity had risen to 79 per cent. This is, however, an exceptional instance for only three patients who have at any time fallen into this group have subsequently recovered sufficiently to be able to work. It is of interest, too, that these were all patients undergoing their first break in compensation. The mortality in this group has been high, 61 per cent. of the cases having died. All of the other patients have remained chronic invalids, showing little clinical improvement after weeks of treatment.

Cardiac patients with a vital capacity which is 40 per cent. of the normal or less are usually bedridden and severely decompensated. Many of them have dyspnea even when completely at rest. Patients whose vital capacity falls as low as this during their first period of cardiac insufficiency may improve so much that they are able to return to a fairly normal life, but the occurrence of such a low vital capacity in later attacks of decompensation makes for a distinctly unfavorable prognosis. Few patients who have at any time fallen into this group have shown great clinical improvement, and more than one half have died.

Table 5 shows the mortality statistics, the number of patients showing evidence of marked decompensation and the number of patients working in each group.

It is evident then, in the light of the foregoing statements, that there is a remarkably close relationship between the clinical condition of cardiac patients, particularly as regards their tendency to dyspnea, and the vital capacity of the lungs. If the vital capacity be known, one can state with a considerable degree of accuracy what the functional condition of the patient probably is. It is, however, not at all surprising that certain exceptions to this rule are found, and that in occasional individual instances the determination of the vital capacity gives a misleading conception as to what may be expected of the sub-

TABLE 5.—THE RELATION OF THE VITAL CAPACITY OF THE LUNGS TO THE CLINICAL CONDITION IN PATIENTS WITH HEART DISEASE *

Group	Vital Capacity, per Cent.	Number of Cases	Mortality, per Cent.	Symptoms of Decompensation, per Cent.	Working, per Cent.
I	90+	25	0	0	92
II	70 to 90	41	5	2	54
III	40 to 70	67	17	53	7
IV	Under 40	23	61	100	0

* Certain cases were tested several times and, owing to changes in the vital capacity they appear in more than one group. In the "mortality" column they are included only in the lowest group into which they fell. "Symptoms of decompensation" indicate dyspnea while at rest in bed or on very slight exertion. Under "working" are included only those actually at work, and able to continue. Many other patients in Group II were able to work, but they are not included as they were still in the hospital.

ject. When one considers that age, body shape, habits of life, exercise and various other factors all tend to make the normal limits of the vital capacity very broad, it is only remarkable that these exceptions are not met with more frequently, and that such a constant correspondence may be found by what is a comparatively rough clinical test. The explanation of this seems to depend on the fact that the normal variations are usually in the direction of an increase above a certain average, while the pathologic variations are in the direction of a decrease. One type of case which may not conform to the general rule of the relation of clinical condition to average vital capacity is that in which the subject has formerly developed an unusually high normal vital capacity and has subsequently acquired heart disease. In such an instance the pathologic lesion in the heart may be associated with a considerable fall of the actual vital capacity, but the relative vital capacity, when compared to average normal standards, remains high. This brings us to a consideration of the changes in the actual vital capacity in the individual case. The various errors which result from the comparison of the individual to average normal standards are thus excluded, and, as might be expected, the variations found are of even more significance.

In many instances several determinations of the vital capacity of the same case have been made at intervals of days, weeks, or months, over long and short periods. The results of these observations may be rather briefly summarized. A very close relationship has been found to exist between the clinical condition and the vital capacity. Decompensated patients show a low vital capacity which rises as improvement begins, and the degree to which the vital capacity increases corresponds well to the degree of clinical improvement. When the vital capacity remains constant the clinical condition remains unchanged.

A rapidly rising vital capacity after a period of decompensation leads to a good prognosis, while failure to rise more than a small amount, and the maintenance of a continuously low vital capacity makes the outlook less favorable. Slight changes in the vital capacity of ambulatory cases may be of much significance. This is well illustrated by the case of J. S., a stained glass worker, who has double mitral disease and auricular fibrillation. When in his best physical condition his vital capacity is 2,600 c.c., or 65 per cent. of the normal. At such times he can walk slowly without discomfort, and can do a little light work. On May 1, 1916, he came to the outdoor department, stating that he felt poorly and found that he was getting out of breath more easily than usual. His vital capacity was found to have decreased to 2,000 c.c., or 50 per cent. He was given digitalis and told to go to bed for a week. On May 19, 1916, he reported again, to say that he was as well as before his upset, and his vital capacity had risen to 2,600 c.c.

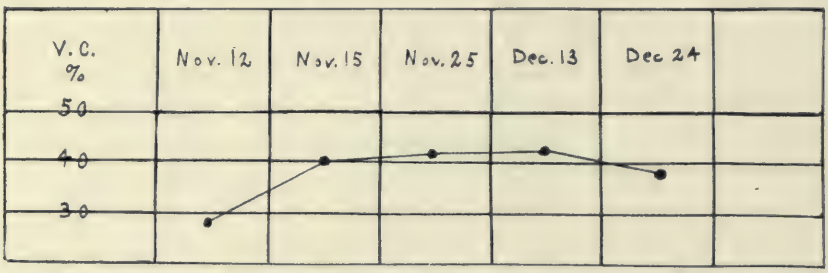

Fig. 5.—M. C. S., showing initial rise in vital capacity after acute cardiac decompensation. Subsequently, the vital capacity remained constantly low. General condition poor.

Figures 5 to 9 show graphically the variations in vital capacity associated with changes in clinical condition. On the basis of the observations as yet made, the impression is quite definite that such charts give a reliable index of the clinical course of the disease. In many ways they are more significant than records of the pulse rate or of the blood pressure, and it is our hope that an extensive routine application of the test of vital capacity may prove to be of distinct clinical value. Medical histories of patients with heart disease abound with vague statements about "dyspnea on exertion," and the increase or decrease of dyspnea, but these are usually only opinions based on the patient's story or on the gross observations of the physician. The importance of such statements would be considerably enhanced if they were confirmed by quantitative graphic methods. Whether, or in how far the determination of the vital capacity will actually fill this need, will only be known after a much larger series of observations than we have yet been able to accumulate has been made.

Two groups of cases, however, in which the determination of the vital capacity has been of service in correcting false impressions derived from the histories, deserve special mention. Several patients, especially women of rather neurotic temperament, have complained of shortness of breath which was apparently quite out of proportion to the physical findings in the examination of the heart, and the vital capacity has been so high as to afford no explanation for such a tendency to dyspnea. On the suspicion that the symptom was due to nervousness and was not true dyspnea, these subjects have been tested by walking rapidly and by climbing stairs. No abnormal dyspnea has resulted, so that the determination of the vital capacity served to con-

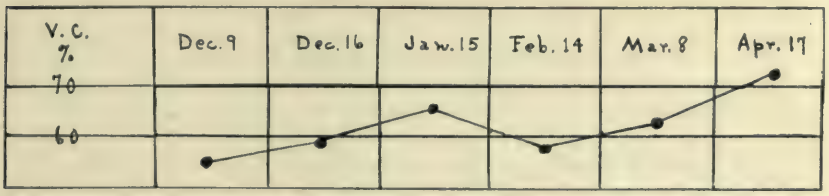

Fig. 6.—W. E. G. The fluctuations in the vital capacity correspond to changes in the clinical condition.

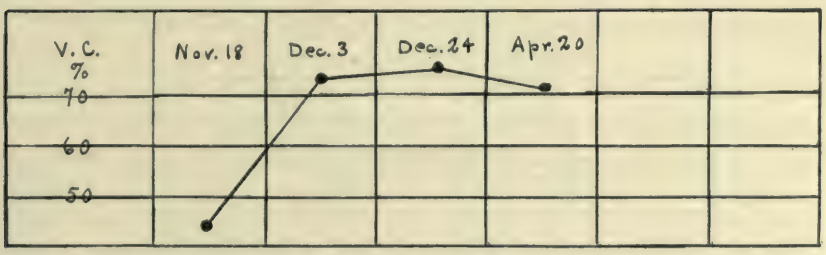

Fig. 7.—I. W. Marked rise in vital capacity, and continued good general condition after acute decompensation.

firm the physical examination, and the history, as given by the patient, could be fairly discounted. On the other hand, a few patients underestimate their respiratory discomfort on exertion. The vital capacity is lower than one would be led to expect from the history, and the lack of dyspnea is difficult to explain. Careful study of such a case, with exercise tests, may demonstrate that the patient's reserve is indeed much less than he has stated, and again the determination of the vital capacity has been a helpful check on the history. In other instances in which the history of dyspnea has seemed out of proportion to the results of physical examination the vital capacity has been low. In these patients the subsequent course has confirmed the value of the history and vital capacity, and has shown that physical examination gave an inadequate conception of the patient's reserve. Thus L. S.

had a vital capacity of 50 per cent. of the normal, but this was considered to be too low and as not representing her true condition. She never made much clinical improvement, however, and died of cardiac insufficiency some months later.

A careful analysis of the cases of heart disease with a view to finding whether there is any relation between the type of lesion and the decrease of vital capacity revealed little of importance. In general the vital capacity tends to be lower in cases with involvement of the mitral valves than in those in which the aortic valves are affected. This agrees with the common clinical observation that dyspnea is a

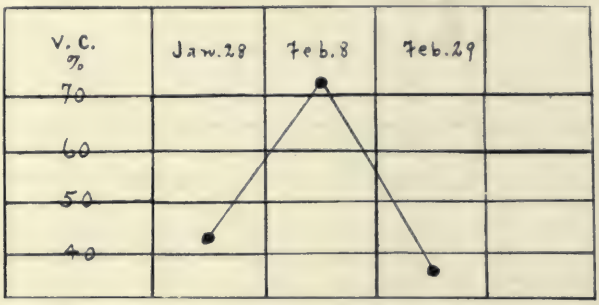

Fig. 8.—M. F. Rise of vital capacity after acute decompensation, and subsequent fall with another attack of cardiac failure.

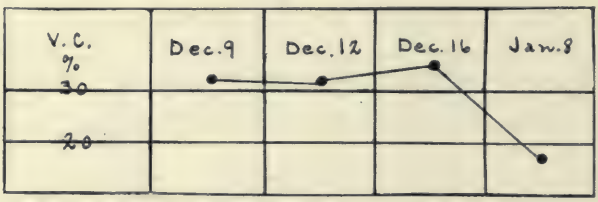

Fig. 9.—F. H. M. Low vital capacity in a patient with marked insufficiency. and further drop just before death.

more prominent symptom in mitral disease than in aortic disease. Beyond this the vital capacity of the lungs seems to depend on the degree of cardiac efficiency; on the severity of the lesion, rather than on the type of lesion.

Cause of the Decrease of Vital Capacity in Heart Disease.—Since the vital capacity of the lungs is the volume of air which can be expired after the deepest possible inspiration, it is evident that any condition which limits the movements of the lungs may be a factor in decreasing the vital capacity. In patients with heart disease a great variety of such conditions may be found. Some of these affect the movement of the chest wall and prevent a normal expansion of the thoracic cavity. Weakness of the intercostal muscles, rigidity of the

bony framework or ankylosis of the costal joints may act in this way. Alterations in the lung tissue itself may cause a diminution in its elasticity, as is seen in emphysema. Accumulations of fluid in the pleural cavities prevent the normal expansion of the lungs, and great cardiac hypertrophy, pericardial effusion or mediastinal tumors may produce a similar result. The normal inspiratory depression of the diaphragm is interfered with by intrathoracic conditions, which make it assume a flattened position even during quiet respiration, and by intra-abdominal conditions which push it upward. Hepatic enlargement, tympanites and ascites are examples of such conditions. Fluid within the bronchi and smaller air passages may prevent the entrance of air into considerable portions of the lung. This is, of course, frequently found in the dependent parts of the lungs in severely decompensated patients. The effect produced by a generalized bronchitis is not wholly clear from the results which we have as yet accumulated. The decrease in vital capacity associated with this condition is frequently much less than one would expect, and observations suggest that the intense dyspnea sometimes occurring in cardiac patients who acquire an acute bronchitis is largely dependent on some factor other than a change in the vital capacity.

In many cases, and particularly in acutely decompensated patients, conditions such as those just mentioned appear to account for the decrease in the vital capacity of the lungs in a wholly satisfactory manner. In other instances, especially where the examination of the heart gives little evidence of insufficiency, and where dyspnea is only experienced on moderate exertion, all of these factors may be absent, and yet the vital capacity may be low enough to fully explain the history of shortness of breath. The cause of the low vital capacity in such cases is not absolutely certain, but the work of Siebeck[7] on the determination of the lung volumes in heart disease bears on the question and suggests that the decrease in vital capacity may be due to an overfilling or engorgement of the pulmonary vessels, and a consequent diminution of the elasticity of the lungs. If this is proved to be true it would signify that the determinations of vital capacity may give direct evidence as to the state of the pulmonary circulation. Such information would be of great value in the study of cardiac insufficiency. Other methods of examination bear chiefly on the greater circulation, and disturbances in the pulmonary circuit are only recognizable when of sufficient grade to cause the passage of fluid out of the vessels into the air spaces and the production of râles.

Experiments have been made to determine whether the decrease in the vital capacity in heart disease is apparent rather than real, and whether the inability to breathe deeply might depend on the rapid rate

of respiration. This would be the case, for instance, if an imperative stimulus to inspire should arise before the end of complete expiration. That this is, however, rarely, if ever, of importance is shown by the fact that patients with a low vital capacity may be able to hold their breath for several seconds at the end of either complete inspiration or of complete expiration.

DISCUSSION

The observations described above indicate that in patients with heart disease there is a close relationship between dyspnea and the vital capacity of the lungs. Thus, in general, patients with a vital capacity of 90 per cent. or more of the normal standard adopted for their sex and height have little or no abnormal tendency to dyspnea. Patients with a vital capacity of from 70 to 90 per cent. of the normal become short of breath on unusual exertion and must lead a restricted life, although many of them can do light work. Patients with a vital capacity of from 40 to 70 per cent. of the normal are much more limited in their activities. They become dyspneic on moderate or slight exertion, are rarely able to work and frequently suffer from cardiac decompensation. Those with a vital capacity of less than 40 per cent. of the normal are decompensated patients, usually confined to bed, and the mortality in this group is high. There is, moreover, a close correspondence in the individual case between changes in the vital capacity and variations in the tendency to dyspnea. In stages of decompensation the vital capacity falls, and with recovery the vital capacity rises. Indeed, comparatively slight changes in the patient's physical condition may manifest themselves in changes in the vital capacity. These facts confirm the evidence in a former paper regarding the importance of the decrease in vital capacity as a factor in the production of dyspnea in heart disease. Various obvious causes of decrease in the vital capacity, such as pleural effusion, emphysema and ascites, have been mentioned and the suggestion has been made that an important factor may be the distention of the pulmonary vessels owing to cardiac insufficiency. If this be true, then the determination of the vital capacity of the lungs may be of value as an early sign of cardiac weakness.

The importance of these observations depends on the relation between the vital capacity and the clinical condition of the patient. It is true that decrease in the vital capacity is only directly associated with a single symptom of heart disease. But this symptom, dyspnea, is a remarkably common one, and the intensity of dyspnea or of the tendency to dyspnea usually follows so closely the clinical course of the disease that it is not infrequently considered a guide to the con-

dition of the patient. It is, in a way, an index of the cardiac reserve, and thus, indirectly, a measurement of the efficiency of the heart. The degree of dyspnea and the tendency to dyspnea are, however, peculiarly difficult to describe accurately or to classify systematically, so that any objective method which will give even approximately exact evidence with regard to dyspnea merits serious consideration by clinicians. The determination of the vital capacity of the lungs, while lacking in absolute quantitative accuracy, is a simple proceeding which appears to do this. The changes in the vital capacity throw interesting light on the course, and often on the prognosis of the disease.

It is important, however, to appreciate that changes in the vital capacity of the lungs are an index of the clinical condition only in so far as the cardiac weakness manifests itself chiefly by causing dyspnea. This is very frequently, but not at all invariably the case. Certain patients with heart disease are restricted in their activities not by becoming dyspneic, but by the occurrence of palpitation or by pain. The vital capacity of the lungs has no direct connection with palpitation or pain, and therefore, in cases in which these are the presenting symptoms, it does not necessarily bear any relation to the clinical condition of the patient.

C. VITAL CAPACITY OF THE LUNGS IN VARIOUS OTHER DISEASES

Although the present study was directed chiefly to a consideration of the vital capacity of the lungs in heart disease, a comparatively large number of observations has been made in other clinical conditions. In some of these a tendency to dyspnea is a common symptom, and in others it is not. Such a series of observations is, of course, of great importance, for it shows in how far the various factors which decrease the vital capacity affect the production of dyspnea in conditions other than heart disease, and also in how far general muscular weakness is an element in causing a decrease of the vital capacity of the lungs. A brief summary of the results obtained in each disease is given below.

Bronchial Asthma.—Many patients with chronic asthma develop an emphysema, and associated with this they are subject to various degrees of dyspnea on exertion. It is thus not surprising to find that the vital capacity may be below normal even in the period between attacks. During the asthmatic attacks the vital capacity becomes much lower. Seven observations on six patients when they were in their best condition between attacks showed the vital capacity to range between 65 per cent. and 122 per cent. of the normal. In only one case was it below 85 per cent. This patient had suffered from asthma for twenty years, became dyspneic easily, and had never been able to do a full day's work. Four patients were tested soon after acute attacks

or at a time when many characteristic râles were present in the lungs. In three the vital capacity was 56, 60 and 85 per cent. The fourth, who stated that she had no dyspnea between attacks, had a vital capacity of 102 per cent. in spite of the presence of a few râles. For obvious reasons it was almost impossible to obtain records of the vital capacity during severe attacks of asthma.

Acute Bronchitis.—In three severe cases of acute bronchitis the vital capacity has not been diminished more than 10 per cent. In a fourth case of uncomplicated bronchitis in a young woman of 24 years, the vital capacity dropped to 76 per cent. of the normal. Objectively, she showed little evidence of dyspnea, but she complained of dyspnea. Several patients with cardiac disease have entered the hospital with extreme dyspnea and a well marked bronchitis. They have, however, not shown a decrease of vital capacity of more than 10 per cent. below the normal figure, and recovery has been rapid. It seems probable that the dyspnea in these cases was due to bronchitis and not to true cardiac decompensation.

Pleural Effusions.—This group includes cases with hydrothorax, pneumothorax, hemothorax, empyema and one instance of carcinoma of the pleura associated with a large pleural effusion. Nine patients have been studied. The vital capacity has been found to vary between 74 and 42 per cent. of the normal. In general the vital capacity seems to depend on the amount of fluid or air in the pleural cavity, and there is a close relationship between the decrease in the vital capacity and the tendency to dyspnea. Some of the patients were extremely sick, and their muscular weakness is probably a factor in lowering the vital capacity.

One patient (T. W.) with a pleural effusion that seemed to fill the left side of his chest, so that the lung was almost completely collapsed, had a vital capacity on two successive days of 48 and 49 per cent. Immediately after thoracentesis, with the removal of 2,200 c.c. of fluid, his vital capacity was still 46 per cent. On the two following days it had risen to 69 and 68 per cent., and three weeks later it was 74 per cent. At this time he could walk about the ward without any sensation of dyspnea, but there were still signs of fluid below the angle of the scapula on the left.

Pneumonia.—No records were obtained on patients during the course of the disease as the pain from the pleuritis makes it impossible for them to take a deep breath. In five convalescent cases, only one of which still showed evidence of pulmonary involvement, the vital capacity was between 71 and 114 per cent. The vital capacity was below normal in three cases, and in them general weakness, persisting after an acute infection, must be taken into consideration.

Cirrhosis of the Liver. — A patient with extensive edema and marked ascites had a vital capacity of 35 per cent. Another advanced case, with great ascites had a vital capacity of 35 per cent., rising to 61 per cent. after the removal of 10 liters of fluid. A man with early cirrhosis of the liver, without ascites, but giving a history of dyspnea on going upstairs (perhaps due to a weak heart) had a vital capacity of 85 per cent. Mechanical interference with the movements of the lungs is the essential factor causing dyspnea in these cases.

Nephritis.—In eight cases of acute nephritis without history of dyspnea, there was no decrease below the normal of the vital capacity. One other patient with acute nephritis, an Arab, had a vital capacity of 71 per cent., but it was impossible to get entirely satisfactory cooperation on the part of the patient, and it is doubtful whether he was breathing as deeply as he could.

In patients with chronic nephritis there is, of course, very frequently an associated involvement of the heart, but it is difficult to say in any individual case exactly how important this feature is. A considerable number of cases of chronic nephritis have been examined, some of them with and some of them without cardiac lesions. In those without evidence of heart disease, and without a history of dyspnea, the vital capacity was high and usually within the normal limits. In the cardiorenal cases, on the other hand, dyspnea was one of the prominent symptoms, and the vital capacity was usually decreased in proportion to the intensity of the dyspnea.

Certain patients with advanced renal disease have a much higher degree of dyspnea than can be explained on the basis of the decrease in the vital capacity alone. Not infrequently an examination of the blood or alveolar air will show a decreased carbon dioxid content. The dyspnea depends in part on an acidosis, and it may be relieved by alkali therapy.

Hyperthyroidism.—Dyspnea on exertion is one of the commonest symptoms complained of by patients with Graves' disease. This may sometimes be the result of nervousness, but it is usually an indication of cardiac weakness. Seven patients were tested, and the vital capacity was above 80 per cent. in five, while in two it was between 67 and 75 per cent. In all the decrease in vital capacity corresponded to the degree of the tendency to dyspnea.

Anemia.—Patients with anemia frequently suffer from dyspnea. Careful analysis of our series of cases, however, showed that weakness was a more common symptom, and in only five out of fourteen patients was a definite history of true dyspnea on exertion obtained. Eleven of these were typical cases of pernicious anemia, two were probably due to carcinoma, and one was secondary to infection with

Dibothriocephalus latus. In eleven cases the vital capacity was 80 per cent. or more, and in two others it was between 70 and 80 per cent. A very emaciated man of 66 years, who was considered to have advanced abdominal cancer, had a vital capacity of 65 per cent. The relation between the tendency to dyspnea and the decrease in vital capacity was not such as to make one consider that the latter was the chief factor in causing dyspnea. It seems more probable that dyspnea in anemia is due directly to the low hemoglobin content of the blood and is of a different mechanism from that in the other conditions which have been considered.

Diseases Unassociated with Dyspnea.—In contrast to the foregoing conditions, thirty patients have been tested who were in the hospital for conditions which are usually not associated with dyspnea. None of the mechanical factors which limit the movements of the lungs were present, and in them the effect of general debility and weakness could be studied. This group of cases includes acute and chronic arthritis, hemiplegia, diabetes, gastro-intestinal diseases, tabes, convalescents from acute infections such as typhoid fever and a number of persons in the surgical wards for slight operations. In twenty-four of the thirty cases the vital capacity was 85 per cent. or more, and in eighteen it was 90 per cent. or more of the normal. It will be well to make brief note of the six patients with vital capacity below 85 per cent. Three of them were diabetics. An emaciated decrepid old man of 69 years had a vital capacity of 63 per cent.; a second patient, so weak that he had to be helped up stairs, had a vital capacity of 76 per cent., and a third patient with diabetes for a year had a vital capacity of 68 per cent., but it was felt that his record was not satisfactory, and did not represent his true vital capacity. A woman, aged 66 years, who probably had peritoneal adhesions, complained of marked dyspnea on exertion and had a vital capacity of 78 per cent. A short man, aged 58, who had vertigo of an unknown cause, but who gave no history of dyspnea, had a vital capacity of 78 per cent. Finally, a young man of 23 years with a chronic synovitis of the knees was found to have a vital capacity of 84 per cent. of the normal. This subject was in bed for practically one year, and had then been on crutches for one year. He has used a cane up to within a week of the time he was tested, and stated that he still became short of breath on hurrying or on going up stairs.

As far as this comparatively small series of patients goes, then, it shows that in the ordinary cases in which dyspnea is not a prominent symptom, the vital capacity is usually within the normal limits. General weakness and debility may account for a slight decrease in the vital capacity, but unless the weakness is extreme it usually does not

cause the vital capacity to drop more than 5 or 10 per cent. below the normal limits. Several patients in whom the vital capacity was below normal were over 50 years of age, and the decrease is in part explained by the normal fall in the vital capacity with advancing years.

SUMMARY

Determinations of the vital capacity of the lungs in a large number of healthy persons has made it possible to establish average normal standards for groups of individuals of different sex and height. When compared to the proper standard the vital capacity of healthy persons very rarely falls below 90 per cent. of the normal standard, although it may rise considerably above the normal.

Observations on patients with heart disease show that there is a close relation between decrease in vital capacity and the tendency to dyspnea. Compensated patients, who do not complain of dyspnea on exertion, have a normal vital capacity. Patients with more serious disease, in whom dyspnea is a prominent symptom, have a low vital capacity, and the decrease in vital capacity runs parallel to the clinical condition. Changes in the clinical condition are usually associated with changes in the vital capacity. As a patient improves, his vital capacity tends to rise, and as he becomes worse, it tends to fall. Determinations of the vital capacity in cases of cardiac disease are often of practical value as they give quantitative information as to the tendency to dyspnea, and thus, indirectly, as to the clinical condition and the reserve power of the patient.

In various other diseases in which mechanical conditions interfere with the movements of the lungs, the tendency to dyspnea corresponds closely to the decrease in the vital capacity. This is, however, apparently not true of the anemias. In diseases in which dyspnea is not a prominent symptom the vital capacity is usually within the normal limits, although general weakness and old age may cause a slight decrease.

CLINICAL STUDIES ON THE RESPIRATION

V. THE BASAL METABOLISM AND THE MINUTE-VOLUME OF THE RESPIRATION OF PATIENTS WITH CARDIAC DISEASE *

FRANCIS W. PEABODY, M.D., JOHN A. WENTWORTH, M.D.
AND
BERTHA I. BARKER
BOSTON

In a recent communication from the Russell Sage Institute of Pathology[1] the first satisfactory observations on the basal metabolism of patients with heart disease were reported. Sixteen patients with cardiac or cardiorenal disease were studied in the bed calorimeter at Bellevue Hospital, New York. An important result of the investigation was the close agreement found in the determination of the metabolism by the direct and indirect methods of calorimetry. Such an agreement, together with the finding of normal respiratory quotients, makes it probable that the metabolism in heart disease is not of an essentially abnormal type, and justifies the use of the indirect method in future work. It was furthermore shown that in patients with compensated cardiac lesions the metabolism was within normal limits, while in patients who had dyspnea while at rest in bed the metabolism was either normal or increased. "Of twelve patients with dyspnea, nine showed a distinct rise in metabolism, and in five of these the increase was from 25% to 50% above the average normal."

The work reported in the present paper is in part a continuation of that done at the Russell Sage Institute, as it seemed worth while to secure more data on so important a subject as the basal metabolism in heart disease. In part, however, it is an extension, for the method used allowed us to obtain information concerning the pulmonary ventilation, and the minute-volume of air breathed. This was of considerable significance to us, since one of the primary reasons which led to the study of heart disease was an interest in the mechanism of the production of dyspnea. It will be readily seen that the minute-volume of air breathed is an important factor in the investigation of patients from this point of view. The greater the amount of air which a patient breathes while at rest, the more limited he will be in his ability

* Submitted for publication April 30, 1917.

* From the Medical Clinic of the Peter Bent Brigham Hospital, and the Medical School of Harvard University.

1. Peabody, Meyer and Du Bois: THE ARCHIVES INT. MED., 1916, **17,** Part II, 980.

to increase his ventilation in response to the rising metabolism accompanying muscular exertion. Thus the greater will be his tendency to become dyspneic easily.

METHOD

The method used in the metabolism experiments was that of Tissot, the spirometer, valves and general technic being essentially as described by Carpenter.[2] Instead of the nose pieces, however, a rubber mask, recommended by Carpenter and made by the Siebe-Gorman Company for their mine rescue apparatus was used. This proved to be a distinct advantage, for the subjects could breathe either through the mouth or nose according to their desire, and in getting reliable records of the minute-volume, it is, of course, essential that the respiration should be as natural as possible. In a few instances the mask could not be adjusted easily and a rubber mouth-piece was used, the nose being tightly clipped. The spirometer was of 100 liters capacity. The experimental periods were usually ten minutes long, but when the minute-volume was particularly high, they were necessarily of shorter duration. The inspired air was piped from outdoors to the inspiratory valves, so that there was no error, as might be the case if room air was used. The analyses of expired air were made with the Haldane portable gas analysis apparatus.[3] The measured volume of expired air was reduced to standard conditions of temperature and barometric pressure, and the calculations were performed in the usual manner.

The metabolism as measured by the heat production in calories per hour was calculated from the oxygen consumption, use being made of the customary table which gives the calorific value of oxygen according to the respiratory quotient. The metabolism was then finally expressed in calories per square meter body surface per hour. The surface area was determined from the height and weight of the patient according to the chart of Du Bois and Du Bois.[4] The average error of this simple method is +1.5 per cent., and the maximum error is only + 5 per cent. Heat production varies of course normally, depending on the age and sex of the subject. The comparison of results in this series of observations has been somewhat simplified by the fact that all the subjects were males. For those between the ages of 20 and 50 years the normal standard of 39.7 calories per square meter of surface area, as given by Gephart and DuBois,[5] has been assumed. For

2. Carpenter: A Comparison of Methods for Determining the Respiratory Exchange of Man, Pub. 216, Carnegie Institution of Washington, 1915.
3. Haldane: Methods of Air Analysis, Charles Griffin & Co., Limited, London, 1912.
4. Du Bois and Du Bois: The Archives Int. Med., 1916, **17,** 863.
5. Gephart and DuBois: The Archives Int. Med., 1916, **17,** 902.

older or younger subjects the average normals given by Du Bois[6] for the various ages have been used. In the tables the metabolism is expressed in the percentage of the appropriate normal.

The general method of conducting the observations was as follows: The patient was brought to the laboratory on the afternoon before the day of the actual experiment. He was then shown the apparatus, the mask was put on his face, and the various experimental manipulations were run through with. This was found to be extremely important, as the subjects were naturally somewhat excited and anxious about what was going to take place. This preliminary trial, however, accustomed them to the method and reassured them completely. On the following morning they were brought to the laboratory in their beds, having fasted since the previous evening. After quieting down for about one-half hour, a record of the normal respiration was taken with a pneumograph. The mask was then adjusted and the metabolism experiment begun. When possible, three continuous ten-minute periods were run, but some of the more sick patients became fatigued after two periods, so that it was necessary to stop the observation. Pneumographic tracings were taken throughout each period, and the average rate of respiration counted. From the volume of expired air the average volume per single respiration was then calculated. The heart rate was counted, without the knowledge of the patient, by means of a stethoscope attached over the precordia.

The clinical condition of the patients on whom this report is based varied greatly. Some had slight valvular lesions, but were otherwise perfectly well, and had no evidence of cardiac decompensation. Others were seriously sick, and suffered from dyspnea and orthopnea. All were propped up in a semireclining position on bed-rests during the observation, but it has been shown that the metabolism is only about 3 per cent. lower in this posture than when lying flat on the back.[7] It is obvious that it is extremely difficult to study the ventilation and the metabolism of patients who are dyspneic or who have a tendency to dyspnea. They are often easily worried by anything like a mask over the mouth or nose, and the psychic condition may alter the type of respiration profoundly. Many patients are wholly unsuitable to work with. The ones reported here are practically picked patients who were intelligent and anxious to cooperate with the work. We can feel reasonably certain that the results indicate the natural conditions.

In a former paper[8] it has been shown that there is a close relationship between the tendency to dyspnea in cardiac patients and the vital

6. Du Bois: The Archives Int. Med., 1916, **17,** 887.
7. Soderstrom, Meyer and Du Bois: The Archives Int. Med., 1916, **17,** 872.
8. Peabody and Wentworth: See page 443, this issue.

capacity of the lungs. This is apparently so generally true that in those cases in which dyspnea is the predominating symptom — and this includes the majority of persons with heart disease — the vital capacity is a peculiarly accurate index of the clinical condition. Patients with a high vital capacity have little or no disturbance from dyspnea, while those in whom the vital capacity is below normal suffer from shortness of breath, and the degree to which they suffer depends largely on the decrease in vital capacity of the lungs. On this basis, then, it has seemed to be of interest in the present study to divide the patients into two groups according to the vital capacity. The first group consists of ten subjects with a vital capacity over 60 per cent. of the normal, according to the standards established by us. The members of this group were in comparatively good clinical condition, all of them being comfortable while at rest, and those whose vital capacity approached normal having little or no dyspnea even with moderate exercise. The second group consists of fourteen patients in whom the vital capacity was 60 per cent. of the normal or less. These were for the most part severely affected persons. Almost all of them became dyspneic on slight exertion, and those whose vital capacity was lowest tended to be dyspneic even while at complete rest in bed. It will be noted in the table that the average size of the patients in the two groups, as measured by their body surface area, is approximately the same.

RESULTS

The essential features of the various observations are shown in detail in the table. It is scarcely necessary to go into a discussion of the individual cases, as a consideration of the average findings in each group brings out clearly the more important results, and there are few significant deviations from the average.

Expired Air.—Analysis of the expired air shows that in Group I the percentage of carbon dioxid is higher and the percentage of oxygen is lower than in Group II. In Group I the carbon dioxid averaged 3.35 per cent. and the oxygen 17.04 per cent., while in Group II the carbon dioxid averaged 2.44 per cent. and the oxygen 18 per cent. Thus in the more severely affected patients the expired air approaches closer to the composition of atmospheric air, and one may say that the inspired air is less effectively used than normally. This is in harmony with the observations of Siebeck,[9] who found that when cardiac patients were made to inspire pure hydrogen, the expired air in the dyspneic, decompensated cases contained a higher percentage of the inspired hydrogen than it did in normal persons or in compensated cardiac cases.

9. Siebeck: Deutsch. Arch. f. klin. Med., 1912, **17,** 252.

BASAL METABOLISM

Case No.	Hospital No.	Name	Date	Surface Area, Square Meters	Vital Capacity, C.c.	Vital Capacity, per Cent. of Normal	CO_2 Tension, Mm.	Number of Periods	Analysis of Expired Air		CO_2 Production per Minute, C.c.	CO_2 Consumption per Minute, C.c.
									CO_2	Oxygen		
1	4800	W. B.	7/11/16	1.73	4,710	98	....	3	3.17	17.52	189	200
2	4724	G. G. S.	6/29/16	1.55	.....	..	....	2	3.24	17.09	183	229
3	4303	M. C.	3/21/16	1.98	3,750	94	....	3	4.15	15.69	227	304
4	4837	M. K.	7/ 7/16	1.94	3,700	93	....	2	2.72	17.77	184	225
5	4295	H. F. T.	3/23/16	1.59	3,770	79	....	2	4.01	16.58	198	221
6	4110	J. C.	2/18/16	1.65	3,170	79	....	2	3.98	16.22	202	252
7	4140	O. G.	2/21/16	1.70	3,700	77	....	2	3.38	17.36	203	221
8	5612	S. G. B.	11/17/16	1.64	2,750	69	....	3	2.70	17.50	149	202
9	5576	W. H. T.	11/11/16	1.69	2,600	65	....	3	2.80	17.66	190	234
10	4258	W. A.	3/ 7/16	1.71	3,050	64	....	2	3.36	17.04	230	280
Average.....				1.72	3,467	..	....	...	3.35	17.04	196	238
11	4373	J. J. McN.	3/28/16	1.96	2,410	60	....	3	2.77	17.51	207	271
12	4151	W. E. J.	2/14/16	1.57	2,280	57	....	3	2.17	18.50	194	227
13	4766	T. W. D	6/28/16	1.69	2,200	55	39.7*	3	2.37	18.26	193	228
14	4262	G. A. L.	3/14/16	1.53	2,080	52	40.7†‡	3	2.83	17.46	158	206
15	4963	F. W. B.	7/12/16	2.03	2,050	51	35.3†§	2	2.44	17.87	238	321
16	4414	S. B.	3/30/16	1.71	1,980	50	....	2	2.42	18.07	192	241
17	4264	C. G.	4/11/16	1.90	2,300	45	....	2	2.51	17.85	168	220
18	4275	G. G.	3/10/16	1.96	2,120	44	....	2	2.31	18.10	230	302
19	5795	M. F. M.	12/19/16	2.14	2,100	44	{30.6* {36.5†	3	2.99	17.16	239	323
20	4411	M. M.	4/ 4/16	1.75	1,990	42	....	2	2.75	17.52	210	277
21	4796	H. B.	7/ 3/16	1.71	1,950	41	....	3	2.59	18.02	198	232
22	5740	R. G.	12/ 9/16	1.56	1,640	41	30.4*	1	2.02	18.43	175	233
23	5704	C. N.	12/ 7/16	1.57	1,475	37	30.4*	1	1.91	18.80	221	259
24	4262	G. A. L.	3/ 2/16	1.70	1,200	30	30.4†‖	2	2.08	18.51	236	291
Average.....				1.77	1,984	..	....	...	2.44	18.00	206	259

* Carbon dioxid tension in alveolar air.
† Carbon dioxid tension in blood (Van Slyke method).
‡ These carbon dioxid determinations were made on June 4, 1916.
§ Blood carbon dioxid taken on July 4, 1916.
‖ Blood carbon dioxid taken on March 4, 1916. Vital capacity had risen on this date to 1,470 c.c. (37.6 per cent.).

DETERMINATIONS

Respiratory Quotient	Calories per Square Meter per Hour	Metabolism in per Cent. of Normal	Minute-Volume, Liters	Rate of Respiration per Minute	Average Volume of Single Respiration	Diagnosis
0.904	35.7	10	6.03	12.7	475	Acute articular rheumatism; mitral insufficiency (?); no symptoms referable to heart
0.799	42.6	7+	5.71	13.4	426	Acute articular rheumatism; mitral insufficiency; heart completely compensated
0.747	43.7	10+	5.52	9.0	639	Chronic myocarditis; aortic insufficiency; mitral insufficiency and stenosis; recovering from decompensation; no dyspnea while in bed
0.818	33.6	5—	6.85	16.3	422	Chronic nephritis; chronic myocarditis and auricular fibrillation; about to be discharged after recovery from decompensation
0.895	44.1	7—	4.99	10.3	457	Acute articular rheumatism; acute serofibrinous pleurisy; chronic myocarditis; slight signs of cardiac insufficiency
0.802	44.0	11+	5.12	8.8	581	Mitral stenosis and insufficiency; auricular fibrillation; chronic arthritis; no evidence of cardiac insufficiency
0.919	38.6	3—	6.07	15.2	400	Mitral stenosis and insufficiency; auricular fibrillation; has recovered from an attack of decompensation and is about to be discharged from the hospital
0.738	35.0	0+	5.58	16.4	342	Chronic nephritis; chronic myocarditis and auricular fibrillation; moderately decompensated heart; walked to hospital on day before this observation
0.812	40.0	1+	6.87	17.6	392	Chronic nephritis with hypertension; chronic myocarditis with slight cardiac insufficiency; no dyspnea except on exertion
0.821	47.4	19+	6.91	12.0	574	Aortic insufficiency; mitral insufficiency; heart well compensated
0.826	....	2.5+	5.97	13.17	471	
0.764	39.4	12+	7.55	22.1	354	Chronic nephritis with hypertension; chronic myocarditis; recovering from acute attack of cardiac insufficiency; no dyspnea while in bed
0.855	42.3	4—	9.07	26.3	346	Mitral stenosis and insufficiency; three days after entering hospital with acute bronchitis; dyspnea on slight exertion; made a rapid recovery
0.847	39.4	1—	8.27	22.1	375	Mitral stenosis and insufficiency; auricular fibrillation; recovering from acute attack of cardiac insufficiency
0.767	38.5	9+	5.65	15.5	341	Chronic nephritis with hypertension; chronic myocarditis; recovering from acute decompensation; no dyspnea while in bed
0.741	44.9	27+	9.91	21.2	469	Chronic nephritis with hypertension; chronic myocarditis; acutely decompensated heart; much edema
0.797	40.6	2+	8.10	27.0	303	Chronic nephritis; syphilitc aortitis and aortic insufficiency; moderately severe decompensation
0.764	33.0	6—	6.78	19.0	355	Chronic nephritis and hypertension; syphilitic aortitis and aortic insufficiency; recovered from severe decompensation; no dyspnea on walking slowly
0.762	43.9	25+	10.10	22.0	479	Chronic nephritis and hypertension; chronic myocarditis; acutely decompensated with considerable dyspnea
0.744	42.8	22+	8.11	13.2	651	Chronic myocarditis and auricular fibrillation; acutely decompensated
0.758	45.1	14+	7.69	18.1	428	Chronic nephritis and hypertension; mitral stenosis and insufficiency; auricular fibrillation; acutely decompensated
0.854	39.4	3—	7.76	20.1	386	Aortic insufficiency; mitral insufficiency; recovering from severe attack of decompensation; no dyspnea while at rest
0.751	42.5	21+	8.81	25.5	346	Chronic myocarditis and auricular fibrillation; acutely decompensated
0.853	48.1	21+	11.80	25.4	465	Chronic nephritis and hypertension; chronic myocarditis; acutely decompensated
0.811	49.4	40+	11.60	27.9	413	Chronic nephritis and hypertension; chronic myocarditis; acutely decompensated
0.791	....	12.8+	8.59	21.8	408	

Carbon Dioxid Production and Oxygen Consumption.—In spite of the difference in the analyses of the expired air the actual production of carbon dioxid and consumption of oxygen per minute does not vary markedly in the two groups of patients. Both carbon dioxid production and oxygen consumption, however, and especially the latter, are somewhat higher in Group II, in which the expired air showed the lower carbon dioxid and the higher oxygen percentages.

Respiratory Quotient.—The respiratory quotients are normal in both groups of cases. The slightly lower quotient (0.79) in Group II corresponds to the higher consumption of oxygen in this group.

Basal Metabolism.—In Group I the metabolism averaged only 2.5 per cent. above the normal figure, and in only one instance (Case 10) was it essentially abnormal. The average metabolism in Group II was approximately 13 per cent. above normal, thus barely above the extreme limits usually set for the normal. Six patients in this group had metabolism of more than 20 per cent. above normal. These determinations of the basal metabolism agree satisfactorily with the results already referred to which were obtained with the large bed calorimeter at the Russell Sage Institute of Pathology. The patients who were in the best general condition (Group I) showed with one exception (Case 10) an essentially normal metabolism, while in the more severely decompensated patients the metabolism was sometimes normal, and sometimes considerably above the normal.

Minute-Volume of Air Breathed.—There is a rather striking difference in the minute-volume of air breathed by the two groups of patients. In Group I the minute-volume averaged about 6 liters, while in Group II it was slightly more than 8.5 liters. There is a general tendency for the minute-volume to be higher in the more severely decompensated members of Group II, in whom the vital capacity is lowest, but this relationship is somewhat obscured by the variation in size of the individual members of the group. G. A. L. was studied twice, first (Case 24) when he was severely decompensated, and later (Case 14) when he was in comparatively good condition and was quite comfortable while at rest. Between these two observations his vital capacity rose from 1,200 c.c. to 2,080 c.c., and his minute-volume fell from 11.6 liters to 5.65 liters, a drop of about 100 per cent. At the same time the basal metabolism showed a decrease of 31 per cent. It would, of course, be natural to associate the high minute-volume in the cases in Group II with an increase of metabolism, but scrutiny of the individual cases shows that such an association does not exist, and a comparison of the average results in the two groups of cases shows that the rise of the minute-volume in Group II is much more definite than is the rise of metabolism. In a few cases the low carbon dioxid

of the alveolar air or blood is evidence of an acidosis, but this is not of sufficiently high grade to account for the rise in minute-volume satisfactorily. This high minute-volume in severely affected cardiac patients has been observed by numerous other investigators among whom may be mentioned Beddard and Pembrey.[10]

Rate of Respiration.—As would be naturally expected, the rate of respiration is considerably higher in the patients whose clinical condition was worst. In Group II the average rate was 21.8, and in Group I it was only 13.2 per minute.

Volume per Respiration.—There is a definite difference between the two groups in the depth of respiration. In Group I the average volume per respiration was 471 c.c., while in Group II it was 408 c.c. Thus the respiration of the subjects of Group II was more rapid and more shallow than it was in the members of Group I.

SUMMARY AND DISCUSSION

Studies of the gaseous metabolism have been made in two groups of patients with heart disease. The subjects of Group I were in good or fairly good clinical condition, while those in Group II were for the most part more severely affected, being either decompensated and dyspneic while at rest in bed or becoming dyspneic on slight exertion. The basal metabolism was slightly higher in the patients of Group II. In some subjects of Group II the increase of metabolism was considerable, but this increase was not constant for all members of the group, and the average heat production per square meter of body surface was scarcely above the normal. On the other hand the minute-volume of air breathed averaged approximately 30 per cent. higher in Group II than it did in Group I, and individual instances were at least double the normal. Closely related to this are other observations which show that in the more seriously sick patients of Group II the rate of respiration is higher, the average volume of respiration is less, and the composition of the expired air approaches more closely to that of atmospheric air than was the case in Group I.

How are these abnormalities in the volume and composition of the expired air to be interpreted? Siebeck[9] has made experiments which have a direct bearing on this subject, and which he explains on the basis that the inspired air is not thoroughly mixed with the alveolar air. Bronchitis, edema, areas of atelectasis, etc., prevent a complete diffusion of the inspired air throughout the lung, so that the efficiency of the respiration is decreased and the inspired air is less completely used than normally. This shows itself in the fact that the expired air

10. Beddard and Pembrey: Brit. Med. Jour., 1908, **2**, 580.

has a high content of the inspired hydrogen in Siebeck's experiments and of oxygen in our own observations. In order, then, to obtain a sufficient amount of oxygen to supply the needs of the metabolism, a larger volume of air must be breathed. It is quite possible that an imperfect mixing or diffusion of the inspired air is a factor in the explanation of these observations, and it is easy to comprehend that such a condition may be present, but there is another feature that appears to be important. The two sets of patients whom we have studied were grouped according to the vital capacity of the lungs, those in Group I having a vital capacity of over 60 per cent., and those in Group II of 60 per cent. or less of our normal standards. Careful study of the minute-volume of the two groups of subjects shows a definite relation between this and the vital capacity of the lungs. In general, as the vital capacity falls, the minute-volume rises. There is, however, no distinct increase in the minute-volume until the vital capacity dropped to 60 per cent. or less of the standards which we have adopted as normal. If the vital capacity is below 60 per cent., the minute-volume is almost invariably increased. Case 14 is an apparent exception to this, but it is explained by the fact that G. A. L. is a small frail man, and the normal standard to which his vital capacity was referred is probably too high. His clinical condition was much better than has been the case with most patients having a vital capacity of only 52 per cent. of the normal, and he can fairly be considered an instance where the comparison of persons to general normal standards leads to an erroneous conception. Such exceptions are, of course, bound to occur.

In general, however, if the vital capacity is as low as 60 per cent. of the normal or less, the minute-volume of air breathed is above normal. Such a decrease in the vital capacity is considerable and is found usually only in rather severely affected patients. Many of the patients had obvious collections of fluid in the pleural cavities, or there was evidence of congestion and edema over the lower portions of the lungs behind, so that the available respiratory surface of the lungs was much diminished. For purposes of comparison with this group a patient may be mentioned with a pleural effusion which apparently filled one side of the chest so that one whole lung was practically completely thrown out. His vital capacity was 48 per cent. It does not seem illogical to assume that in these patients of Group II with much decreased vital capacity the respiratory surface is similarly diminished. The "dead space," however — nasopharynx, oropharynx, trachea, large bronchi, etc. — in which there is no respiratory exchange, probably remains essentially unchanged. The volume of each respiration is less than normal (408 c.c. in Group II as opposed to 471 c.c.

in Group I), but the dead space being unchanged, a much smaller proportion of each respiration reaches the alveoli. In order, however, that a normal or slightly higher than normal amount of oxygen shall be taken up by the blood in the alveolar walls, so as to keep pace with the metabolism of the body, the rate of respiration is increased. The expired air contains less carbon dioxid and more oxygen than normal, because it contains a larger proportion of air from the dead space.

The various abnormal findings in patients with severe heart disease can thus be explained on the basis of a decrease in the vital capacity of the lungs associated with a diminished respiratory surface. The volume per respiration is decreased, but the dead space is probably unchanged, so that the proportion of each inspiration remaining in the dead space is relatively increased. Oxygen supply is kept up by raising the rate of respiration, and in order that the alveolar ventilation may remain sufficient in spite of the relative increase of "dead space" the minute-volume of air breathed must be increased.

These observations on the increased minute-volume in patients with severe heart disease have a practical bearing on the production of dyspnea. If a normal person walks at a moderate pace the metabolism rises and the minute-volume is increased perhaps fourfold. With a patient in Group I it might thus rise from 6 to 24 liters. This is not a large amount, and a person with a normal vital capacity who can increase the depth of respiration easily would have no discomfort on breathing such a volume. If, however, one of the patients in Group II performed similar exercise, the minute-volume in his case, likewise rising fourfold, would amount to over 34 liters. This is much higher than it was with the more normal subject of Group I, and it thus is more difficult to maintain. It is, moreover, especially difficult for the subject in Group II, for his vital capacity is low and he cannot breathe deeply. It will thus be seen that the lower the minute-volume of air breathed at rest the less will be the tendency to dyspnea on exertion and the greater will be the patient's reserve. In like manner the slower the rate of respiration at rest, the greater will be the reserve. Thus an increase of the minute-volume of air breathed while at rest, and an increase in the rate of respiration while at rest, may both be factors in the production of dyspnea in heart disease.

CONCLUSIONS

Observations are reported on the gaseous metabolism and pulmonary ventilation of two groups of patients with heart disease. Group I consists of subjects in good or fairly good condition, in whom the vital capacity of the lungs was over 60 per cent. of the normal. Group

II consists of much more severely affected patients in whom the vital capacity was 60 per cent. of the normal or less.

The basal metabolism calculated from the oxygen consumption per square meter of body surface averaged 2.5 per cent. above normal in Group I, and 12.8 per cent. above normal in Group II.

The average volume per respiration was less in Group II than in Group I, and the average rate of respiration was higher in Group II than in Group I.

The minute-volume of air breathed averaged approximately 30 per cent. higher in the members of Group II than it did in those of Group I.

The relation is pointed out between the increase of the minute-volume of the more seriously affected patients and the decrease in the vital capacity of the lungs.

Finally it is shown that this high minute-volume is a factor in the production of dyspnea in persons with severe heart disease.

BOOK REVIEWS

A Monograph on the Epidemic of Poliomyelitis (Infantile Paralysis) in New York City in 1916. Based on the Official Reports of the Bureaus of the Department of Health. Published under the direction of the Department of Health of New York City. 1917.

To the many physicians throughout the country who followed with intense interest the poliomyelitis epidemic of 1916, this Monograph from the Department of Health of New York City cannot fail to be welcome. The size of the report—some 400 pages—would at first glance suggest redundancy, but one fails, in reading through it, to find anything which is not of interest and importance. Although compiled primarily from the standpoint of public health, all phases of the subject are well discussed from the purely scientific side as well, the attitude throughout being critical and conservative.

The first section, which is entitled "Historical," tells the story of the outbreak of the disease. The realization of the unusual severity of the epidemic, and the consequent emergency organization to study and control the disease, are related in detail. The arrangements for quarantine, publicity, and hospital care, the enrolment of special physicians and visiting nurses, the establishment of special poliomyelitis clinics, and the literature for lay distribution, may be mentioned among the many points to which attention was paid.

In the chapter on etiology are summarized both the pre-existing ideas as well as the points brought out by study of this epidemic. The finding of the virus in dust and sweepings, its resistant character, and the almost inescapable assumption of the intermediate human carrier, are discussed. A conservative statement of the status of the bacteriology of the disease is presented, and finally, the reemphasis by this epidemic of the paramount importance of the "abortive" or "nonparalytic" cases of the disease is dwelt on with due weight.

The chapter following, on epidemiology, considers in detail the various factors of possible importance in the spread of the disease. Season, sex, and age, sources of infection, food and milk supply, domestic animals as possible carriers, are discussed, and a separate section is devoted to a careful consideration of the possible association of insect carriers with the disease. The actual data of the epidemic are then presented, with charts, maps, and tables.

In the section on pathology one notes with special interest the frequent mention of nasopharyngeal lesions, which would harmonize well with the idea of transmission of the disease by the buccal secretions. In discussing the symptomatology, the importance is emphasized of the cases which run their course without paralysis.

The section on diagnosis presents an elaborate study of the spinal fluid findings. The increased cell count early in the disease, the late persistence of the globulin, and the colloidal gold curves are discussed. One is pleased to see that no rigid diagnostic claims are made, the interpretation of the findings in connection with the clinical picture being insisted on.

The chapter on treatment presents of course a disappointing record. The high mortality emphasizes the inability of the present therapeutic methods to cope with the disease even when recognized early. A thorough trial of all methods which seemed reasonable was, however, made, and one reads with particular interest of the studies on serumtherapy. As is, unfortunately, so often the case, a measure sound theoretically actually gives disappointing results, owing to such practical difficulties as that of getting the patients under treatment at the very onset.

The volume concludes with photographs and interesting charts illustrating the spread of the epidemic.

THE DIAGNOSIS AND TREATMENT OF ABNORMALITIES OF MYOCARDIAL FUNCTION; WITH SPECIAL REFERENCE TO THE USE OF GRAPHIC METHODS. By T. Stuart Hart, A.M., M.D., Assistant Professor of Clinical Medicine, College of Physicians and Surgeons, Columbia University. Price, $4.50. Pp. 320. 248 illustrations. New York. Rebman Company, 1917.

Dr. Hart has made a definite contribution to electrocardiographic literature in this book. To the physician in hospital or general practice the variations in rate, rhythm and conduction are presented in an interesting and comprehensive manner. The preliminary discussion of cardiac physiology and pathology and their relation to graphic methods of registration furnishes the student with the information necessary for the proper interpretation of polygraphic and electrocardiographic records. A description of the instruments employed and of the details of their manipulation are available from other sources and have been wisely omitted by the author; so also have many theoretical considerations which still belong to the sphere of experimental cardiac pathology.

Bradycardia, tachycardia, heart block, extrasystoles, flutter and fibrillation are discussed with regard to their mechanism, experimental production, pathology, etiology, symptoms, identification and clinical significance. The presentation of the subject matter is clear and systematic. References are frequently made to the experimental data on which much of our knowledge is based. The clinical manifestations are constantly brought to the reader's attention and associated with the electrocardiographic picture.

The chapters on paroxysmal tachycardia, fibrillation and flutter are of particular interest. The close etiologic relationship between these three conditions is substantiated by electrocardiograms taken during the transition from one to another. The influence of right and left vagal stimulation on the cardiac rhythm is also well illustrated by graphic records. Bundle branch block, however, receives but passing mention and no electrocardiograms are included which show the atypical R waves associated with subendocardial lesions of the ventricular musculature.

In discussing sino-auricular block, phasic variation of rate and irregularities of the whole heart, the author does not agree with other investigators who believe that a partial or complete interruption of the excitation wave at the sino-auricular node may account for some of these phenomena. Since the publication of this book, Eyster and Meek have reported experiments in which partial sino-auricular block has been successfully produced in the dog's heart, confirming the view that in the human heart the sino-auricular node may be the seat of partial or complete obstruction. In view of these findings the interpretation of Figures 164 to 174 might bear revision.

The later chapters deal with the treatment of cardiac disease. Emphasis is placed on individualization in prognosis and treatment and on the conservation of myocardial reserve rather than on specific lines of therapy. The bibliography is carefully selected and classified. A conspicuous feature of the publication is the large number of excellent illustrations. The variety of conditions illustrated by polygrams and electrocardiograms is evidence of the wide experience of the author and demonstrates the importance of graphic studies in relation to the diagnosis and treatment of myocardial disorders.

CONTENTS OF VOLUME XIX

APRIL, 1917. NUMBER 4

The Effect of Muscular Work, Diet and Hemolysis on the Serum Proteins. A. H. Rowe, M.D., Oakland, Calif.

The Causes of the Variation in the Concentration of Urea in the Blood of Young, Healthy Adults. T. Addis, M.D., and C. K. Watanabe, M.D., San Francisco.

Autotransplantation and Homotransplantation of the Thyroid Gland, Using the Capsule as the Seat of Transplantation. J. H. Hess, M.D., and A. A. Strauss, M.D., Chicago.

The Effect of Salicylates on Experimental Arthritis in Rabbits. B. Fantus, M.D., W. E. Simmonds, M.D., and J. J. Moore, M.D., Chicago.

A Case of Infundibular Tumor in a Child, Causing Diabetes Insipidus with Tolerance of Alcohol. L. Newmark, M.D., San Francisco.

Roentgenography of the Lungs. Roentgenographic Studies in Living Animals After Intratracheal Injections of Iodoform Emulsion. C. A. Waters, M.D., S. Bayne-Jones, M.D., Baltimore, and L. G. Rowntree, M.D., Minneapolis.

The Reactivated Thymus. G. H. Hoxie, M.D., Kansas City, Mo.

A Study of the Diastatic Activity of the Urine and Feces with Special Reference to Diseases of the Pancreas. C. W. McClure, M.D., and J. H. Pratt, M.D., Boston.

The Suprarenal System and Carbohydrate Metabolism. G. M. Mackenzie, M.D., New York.

A Study of Ethylhydrocuprein (Optochin) in the Treatment of Acute Lobar Pneumonia. H. F. Moore, M.B., B.Ch., and A. M. Chesney, M.D., New York.

MAY, 1917. NUMBER 5. PART I

An Experimental Test of the Relation of Sewage Disposal to the Spread of Pellagra. J. F. Siler, M.D., P. E. Garrison, M.D., and W. J. MacNeal, M.D., New York.

Intestinal Eosinophilia, with Report of a Case. G. D. Barnett, M.D., San Francisco.

The Significance of Embryonal Fat Cells in Certain Pathologic Conditions. D. Symmers, M.D., and A. Fraser, M.D., New York.

Experimental Appendicitis. J. W. McMeans, M.D., New York.

The Influence of the Radiations from Kromayer's Mercury Quartz Lamp on the Cerebral Cortex (Animal Experiments). H. Wago, M.D., Tokio, Japan.

The Carbon Dioxid Content of Blood and of Alveolar Air in Obstructed Expiration. E. D. Friedman and H. C. Jackson, New York.

A Study of Blood Sugar. A Comparison of the Tolerance for Glucose in Diabetic and Normal Subjects. R. Cummings, M.D., and G. Piness, M.D., Los Angeles.

The Reflex Action of Volatile Irritants on the Circulation. C. C. Lieb, M.D., and W. W. Herrick, M.D., New York.

Transient Heart Block — Electrocardiographic Studies. E. B. Krumbhaar, M.D., Philadelphia.

The Human and Animal Liver After Alcohol. F. A. McJunkin, M.D., Milwaukee, Wis.

MAY, 1917. NUMBER 5. PART II

Clinical Calorimetry. Nineteenth Paper. The Basal Metabolism of Old Men. J. C. Aub, and E. F. DuBois, M.D., New York.

Clinical Calorimetry. Twentieth Paper. The Effect of Caffein on the Heat Production. J. H. Means, M.D., Boston, J. C. Aub, M.D., and E. F. DuBois, M.D., with the Technical Assistance of G. F. Soderstrom, New York.

Clinical Calorimetry. Twenty-First Paper. The Basal Metabolism of Dwarfs and Legless Men, with Observations on the Specific Dynamic Action of Proteins. J. C. Aub, M.D., and E. F. DuBois, M.D., with the Technical Assistance of G. F. Soderstrom, New York.

Clinical Calorimetry. Twenty-Second Paper. The Respiratory Metabolism in Nephritis. J. C. Aub, M.D., E. F. DuBois, M.D., with the Technical Assistance of G. F. Soderstrom, New York.

Clinical Calorimetry. Twenty-Third Paper. The Effect of Roentgen-Ray and Radium Therapy on the Metabolism of a Patient with Lymphatic Leukemia. J. B. Murphy, M.D., New York; J. H. Means, M.D., Boston, and J. C. Aub, M.D., New York.

Clinical Calorimetry. Twenty-Fourth Paper. Metabolism in Three Unusual Cases of Diabetes. F. C. Gephart, Ph.D., J. C. Aub, M.D., E. F. DuBois, M.D., Graham Lusk, Sc.D., with the Technical Assistance of G. F. Soderstrom, New York.

Clinical Calorimetry. Twenty-Fifth Paper. The Water Elimination Through Skin and Respiratory Passages in Health and Disease. G. F. Soderstrom and E. F. DuBois, M.D., New York.

JUNE, 1917. NUMBER 6

Hay-Fever and Hay-Fever Pollens. William Scheppegrell, M.D., New Orleans.

The Systolic Blood Pressure Following Exercise; with Remarks on Cardiac Capacity. D. L. Rapport, Boston.

A New Interpretation of the Pathologic Histology of Hodgkin's Disease. Douglas Symmers, M.D., New York.

The Treatment of Syphilis of the Central Nervous System. A Comparison of Mercurialized Serum and Salvarsanized Serum. David A. Haller, M.D., Boston.

The Salicylates. VI. Renal Function and Morphologic Changes in Animals Following the Administration of Salicylate. Paul J. Hanzlik, M.D., and Howard T. Karsner, M.D., Cleveland.

The Salicylates. VII. Further Observations on Albuminuria and Renal Functional Changes Following the Administration of Full Therapeutic Doses of Salicylate. Paul J. Hanzlik, M.D., R. W. Scott, M.D., and T. W. Thoburn, A.B., Cleveland.

The Influence of Nonspecific Substances on Infections. James W. Jobling, M.D., Nashville, Tenn.

The Effect of Pituitary Injections on the Blood Pressure of Febrile Patients. Harry B. Schmidt, Ann Arbor, Mich.

Diminished Blood Platelets and Marrow Insufficiency. A Classification and Differential Diagnosis of Purpura Hemorrhagica. Aplastic Anemia and Allied Conditions. George R. Minot, M.D., Boston.

The Reaction of the Cerebrospinal Fluid. Preliminary Report on Hydrogen-Ion Concentration as Determined by the Colorimetric Method. Lloyd D. Felton, M.D., R. G. Hussey, M.D., and S. Bayne-Jones, M.D., Baltimore.

CONTENTS

PAGE

THE ETIOLOGIC AGENT OF RAT BITE DISEASE. PRELIMINARY REPORT. J. KITAGAWA, M.D., AND T. MUKOYAMA, M.D., NAGOYA, JAPAN 317

THE SALICYLATES. VIII. SALICYL EDEMA. P. J. HANZLIK, M.D., R. W. SCOTT, M.D., AND J. L. REYCRAFT, M.D., CLEVELAND 329

A STUDY OF POLIOMYELITIS. REPORT OF THE WORK OF THE MENINGITIS DIVISION OF THE RESEARCH LABORATORY IN THE 1916 EPIDEMIC. JOSEPHINE B. NEAL, M.D., HARRY L. ABRAMSON, M.D., AND ASSOCIATES, NEW YORK 341

FURTHER STUDIES WITH THE SCHICK TEST. ABRAHAM ZINGHER, M.D., NEW YORK 392

THE EFFECT OF UNDERNUTRITION ON MUSCULAR FORCE. A STUDY OF THE INFLUENCE OF LOW DIETS, OR THE ALLEN METHOD OF TREATMENT, ON THE PHYSICAL VIGOR OF DIABETICS. JOHN R. WILLIAMS, M.D., ROCHESTER, N. Y. 399

AURICULAR FLUTTER. A CONSIDERATION OF SOME PROBLEMS ARISING IN THE STUDY OF A CASE, AND OF THE LITERATURE. JAMES D. HEARD, M.D., PITTSBURGH, AND ARTHUR E. STRAUSS, S.B., M.D., ST. LOUIS 409

CLINICAL STUDIES ON THE RESPIRATION. III. A MECHANICAL FACTOR IN THE PRODUCTION OF DYSPNEA IN PATIENTS WITH CARDIAC DISEASE. FRANCIS W. PEABODY, M.D., BOSTON 433

CLINICAL STUDIES ON THE RESPIRATION. IV. THE VITAL CAPACITY OF THE LUNGS AND ITS RELATION TO DYSPNEA. FRANCIS W. PEABODY, M.D., AND JOHN A. WENTWORTH, M.D., BOSTON 443

CLINICAL STUDIES ON THE RESPIRATION. V. THE BASAL METABOLISM AND THE MINUTE-VOLUME OF THE RESPIRATION OF PATIENTS WITH CARDIAC DISEASE. FRANCIS W. PEABODY, M.D., JOHN A. WENTWORTH, M.D., AND BERTHA I. BARKER, BOSTON 468

BOOK REVIEWS:

A MONOGRAPH ON THE EPIDEMIC OF POLIOMYELITIS (INFANTILE PARALYSIS) IN NEW YORK CITY IN 1916 479

THE DIAGNOSIS AND TREATMENT OF MYOCARDIAL FUNCTION, WITH SPECIAL REFERENCE TO THE USE OF GRAPHIC METHODS. BY L. STUART HART, A.M., M.D. 480

THE ARCHIVES OF INTERNAL MEDICINE is issued monthly. Two volumes are published annually.

Manuscripts offered for publication and other correspondence relating to the editorial management of THE ARCHIVES should be sent to Dr. Joseph L. Miller, 122 South Michigan Boulevard, Chicago. Communications regarding subscriptions, reprints, etc., should be addressed to THE ARCHIVES OF INTERNAL MEDICINE, American Medical Association, 535 North Dearborn Street, Chicago.

Footnotes and bibliographies should conform to the style of the Index Medicus or to that of the Index-Catalogue of the Surgeon General's Library. It is specially requested that the titles of articles and the exact date of issues, year, volume and page, be given in each case. Contributors are requested not to furnish bibliographies which are unnecessary, or mere clerical compilations. On receipt of 10 cents the American Medical Association will send a pamphlet entitled "Suggestions to Medical Authors," containing suggestions to authors on the preparation of manuscripts, rules for footnotes and bibliographies and a list of several hundred medical periodicals of the world, with approved abbreviations of each.

Authors will receive one hundred reprints free; additional copies may be obtained at cost.

The domestic subscription price per year of two volumes is $4.00; Canadian rate $4.25; foreign rate $4.40 (18 shillings, 18 marks, 22 francs); including postage. Single copies 50c postpaid.

Make checks, etc., payable to the AMERICAN MEDICAL ASSOCIATION.